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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

JULY, 1943

ROLE OF THE KIDNEY IN THE GENESIS OF HYPERTENSION*

HOMER W. SMITH, WM. GOLDRING AND HERBERT CHASIS

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My position on this program is suggestive of the role of an intermediary between exploratory investigation and practical medicine. Whether or not it was the intention of the program committee, I am sandwiched between theory and practice and shall endeavor to discharge my responsibilities by discussing the evidence for and against the belief that the kidneys are primarily responsible for the genesis of essential hypertension.

For some years a group of investigators at New York University College of Medicine have been studying this question from the point of view of the renal circulation. William Goldring, Herbert Chasis and Hilmert Ranges are the investigators concerned, and I must emphasize to you that I appear here tonight merely in the capacity of a spokesman for my colleagues. Not only am I indebted to them with respect to published investigations, but at my request Goldring and Chasis have prepared for me the digest of literature which I shall later review. Needless to say, however, we are in complete agreement in respect to interpretation and I gladly assume the responsibility for what I have to say.

* Read at the Stated Meeting of The New York Academy of Medicine, February 4, 1943.

As a physiologist and a neutral observer of the pros and cons in the long-standing debate on the role of the kidney in hypertension, I have no subjective reasons for pulling my punches.

Last year we published a study of the effective renal blood flow in sixty subjects with essential hypertension, many of whom had been followed for a considerable period of time.[1] We emphasized that the renal blood flow by itself is an unreliable datum since the quantity of functional renal parenchyma in various individuals, and especially in individuals with diseased kidneys, varies considerably. Consequently in that report the quantity of functional renal parenchyma present in each subject was evaluated by means of the saturation method and the effective blood flow was in each case referred to this primary datum. The resulting ratio of the effective blood flow per unit of residual functional tissue is remarkable for its constancy in normal subjects, and it constitutes an index to which considerable significance, in our opinion, may be attached in subjects with vascular or renal disease.

Omitting the finer technicalities of that study, we concluded that our evidence was against the belief that renal ischemia exists primary to the development of essential hypertension. It is true that renal ischemia is present in many hypertensive subjects, but this ischemia appears to be a result of the presence of vasoconstrictor substances in the blood, since it is readily reversible by agents which produce renal hyperemia in normal subjects, and during induced hyperemia the effective blood flow per unit of functional rental tissue is of the same order of magnitude in hypertensive subjects as in normals. The ischemic tendency is still present after renal denervation, which is why we think that it is of humoral origin.

It does not advance our problem, and it is of course illogical, to suppose at one moment that humoral agents are operating to reduce renal blood flow and then at the next moment to suppose that the reduction in renal blood flow is the reason for the appearance of these agents in the blood.

An even more cogent line of evidence is available in a second study made by Chasis and Redish[2] of the effective renal blood flow in the separate kidneys of twenty-one hypertensive patients. If it is predicated that renal ischemia is the primary causal factor underlying essential hypertension, the factors giving rise to this ischemia must be sought in anatomical faults which obstruct some greater or lesser fraction of the

renal circulation. By the laws of chance, and in accordance with the experience of pathologists, such obstructions would not be distributed symmetrically nor would they, except in rare instances, affect the renal blood flow symmetrically. Consequently, unilateral ischemia should be observed much more frequently than symmetrical bilateral ischemia. Yet among these twenty-one hypertensive patients the effective blood flow per unit of functional tissue was, within limits of variability no greater than are observed among normals, identical on the two sides. Not a single one showed unilateral impairment. This result is compatible only with the view that the ischemic tendency operates equally upon the two kidneys, and it is difficult to see how this could be the case if ischemia *per se* is the beginning of the story.

Proponents of the ischemic theory sometimes obscure the argument by hypothesizing that in essential hypertension a multitude of microscopic Goldblatt clamps have been placed upon the finer renal arterioles. But this is a begging of the question. If we are to respect the meaning of words and the sequences of pathology, then those who would put clamps upon all or a large fraction of the renal arterioles must forthwith abandon the primacy of renal ischemia in the argument of causation, and accept the primacy of arteriolar disease of as yet unidentified origin.

To summarize these clinical studies, then, the renal ischemia which is present in some hypertensive subjects affects both kidneys equally; it is of a physiological, reversible nature except in very late stages, and under reversal a hyperemia as good as is enjoyed by normal kidneys results; it appears to be of humoral origin, since denervation does not abolish it. Faced with these facts we interpret the observed renal ischemia as one of the sequelae of the disease, and not its cause. The renal arterioles in man appear to be rather more sensitive normally to vasoconstrictor agents than they are in the dog, the only other well-studied species. It would be profitable, perhaps, to make in man a quantitative study of the relative sensitivity of the renal arterioles as compared with those of the skin and muscle mass.

From this point, then, let us reword our problem by asking what is the evidence that the kidneys play any part in the origin of hypertension? There comes to your mind immediately, no doubt, the Goldblatt experiment, and I would answer this apparently convincing argument by saying that this is only reasoning by analogy. I will reply by drawing an analogy. Had someone applied a clamp to the pancreatic

artery before the days of Minkowsky and obtained diabetes (and I have no doubt but what the judicious application of a clamp to the pancreatic artery would produce some form of diabetes or at least glycosuria), there would have come into existence the theory that diabetes was due to pancreatic ischemia. We know, of course, that that is not so and indeed it is probably the very rare case in which pancreatic ischemia plays any part. When Minkowsky took out the pancreas and obtained diabetes, there came into existence the theory that diabetes in the historic and literal sense of glycosuria, is due solely and simply to an underproduction of insulin. We now know that this is not true. The essential clinical signs and symptoms commonly identified as diabetes, i.e., decreased glucose tolerance and glycosuria, may be brought into existence by disturbances in the pituitary gland, in the liver, and possibly in the adrenal cortex, in animals and individuals in which the pancreas is not primarily at fault, whatever intermediary role the pancreas may play. What, then, are the causes of diabetes? They are multiple, and in no instance do we yet know the whole answer. The Goldblatt experiment shows that you can produce hypertension in the dog by renal ischemia. The experiment in principle is unquestionably applicable to man, but it proves nothing logically about the sequence of events in that large group of patients who have so-called "essential hypertension."

What other evidence is there to indict the kidneys? There come to mind numerous papers published in the last few years which, whatever their intent, give the impression of demonstrating that unilateral renal disease is causally related to a hypertensive process. The proof consists in the purported reduction of the hypertension by the removal of the offending kidney. There is, unfortunately, no criterion of the presence or intensity of hypertensive disease except the elevation of the blood pressure itself, or the subjective distress and eye-ground changes which are presumed to be sequelae of the elevated blood pressure; and blood pressure is an extraordinarily complex dynamic product of the circulation in which changes are difficult to interpret even under optimal conditions for the most precise study. I need not dwell upon the lability of the blood pressure in many hypertensive subjects, since this lability has been discovered by every investigator who has attempted to work under controlled conditions.

But because of the importance which this surgical-pathological literature assumes in the general impression, I have asked my colleagues

TABLE I

UNILATERAL NEPHRECTOMY

Papers.....25	*Cases*	*Per cent*
Cases	76	100
Negative results reported	39	51
Positive results reported	37	49
Of these, 30 are incorrectly appraised because:		
a. BP did not fall into normal range	8	27
b. Inadequate control	1	3
c. Inadequate postoperative follow-up	19	63
d. BP returned to hypertensive level in 6 months	2	7
Final appraisal: Negative results	69	91
Positive results	7	9

to review it *in toto* and to appraise it critically under rigid but reasonable specifications.*

It is convenient to break this literature into several categories, the first of which consists of those papers, 25 in number,[3-27] in many of which a reduction in blood pressure has been reputed to follow unilateral nephrectomy, the removal of the kidney being indicated by demonstrated or suspected unilateral renal disease (Table I). Seventy-six cases are reported in these 25 papers, and in 51 per cent of these cases the authors themselves report negative results in respect to blood pressure reduction. Of the 49 per cent in which a positive result was obtained in the authors' opinion, 30 cases are held by my colleagues to be incorrectly appraised either because the blood pressure did not fall into the normal range, because there was an inadequate control study to establish true hypertension, because there was inadequate postoperative follow-up, or because the blood pressure was shown to return to hypertensive levels within six months. So in the final appraisal, out of the total of these 76 cases, unilateral nephrectomy has had a favorable result in respect to the reduction in blood pressure in 7 cases only.[3, 7, 9, 14, 17, 18, 19] Accepting these 7 cases on their face value, in only one case in ten in which the thesis has been tested by nephrectomy is there evidence that the hypertensive process has its origin in disease of one kidney.

* A detailed discussion of criteria, etc. will appear in a subsequent publication.

TABLE II

ALLEGED COMPRESSION OF THE RENAL ARTERY OR RENAL PARENCHYMA

Obstruction of renal artery	7
Renal compression	3
Total	10
Hypertension may have preceded plaque	1
Questionable compression of renal artery by aortic aneurysm	1
Bilateral renal disease not excluded	2
Blood pressure did not fall after nephrectomy	2
Unsatisfactory	6
Apparently satisfactory	only 4 in entire literature

The second category deals with instances of hypertension supposedly arising from mechanical compression of the renal circulation or the renal parenchyma (Table II). There are a total of 10 cases in the literature,[6, 7, 15, 17, 27, 28, 29, 30, 31, 32] seven of which had obstruction of one sort or another of the renal artery, while 3 had renal compression. On reviewing these records, one must be discarded because there was a possibility that hypertension may have preceded the formation of the plaque which at necropsy was discovered in the renal artery; one was a suppositious compression of the renal artery by an aortic aneurysm, but being suppositious, is scarcely admissable as positive evidence. In two cases bilateral renal disease was not excluded, and in one of these it was quite definitely indicated. In two cases the blood pressure did not fall after nephrectomy, indicating that when put to the final test the assumed explanation failed to work. This leaves us with 4 cases only in the entire literature in which apparently satisfactory correlation is established between gross obstruction of the renal circulation and hypertension. We accept these 4 cases at their face value as demonstrating the applicability of the Goldblatt experiment to man, without generalizing beyond the limited evidence.

Turning now to the other aspects of the problem, we come to the third category of papers in which it is claimed that there is an abnormally high incidence of urologic disease in hypertensive subjects (Table III). Schroeder and Steele[33] have reported 113 urologic anomalies out

TABLE III

INCIDENCE OF UROLOGIC DISEASE IN HYPERTENSION

Schroeder and Steele (1941) report 113/250 positives among living patients, or 45 per cent. Of these:

53 had bilateral renal disease:
8 had glomerulonephritis
17 had bilateral abnormal pyelogram
28 probable renal disease

Leaving 60/250 possible unilateral disease, or 24 per cent.

Wosika, Jung and Maher (1942) report 227/568 positives in necropsies, or 40 per cent, including all types of unilateral and bilateral disease, with no break-down.

of 250 living patients with hypertension, or a 45 per cent incidence of urologic fault. We exclude from this list 53 who had bilateral renal disease; 8 who had glomerulonephritis, 17 with bilaterally abnormal pyelograms, and 28 in whom renal disease was suspected but not proven. This leaves 60 patients with apparent urological fault out of 250 hypertensives, or 24 per cent. However, the judgment of urologic fault in this series was based largely upon abnormal radiograms obtained by intravenous or retrograde pyelography, and it has been our experience that the diagnosis of abnormality in a pyelogram is a very hazardous matter, since an innocuous angulation of the ureter or dilatation of the pelvis can give the visual impression of significant abnormality, although there is actually no obstruction of the lumen or evidence of renal impairment. The incidence of such apparent abnormalities in adults giving no history or evidence of abnormal renal function or of hypertension is very large. The significance of many of the residual 60 cases in Schroeder and Steele's series is therefore open to some doubt.

Wosika, Jung and Maher[34] have reported 227 urologic abnormalities out of 568 necropsies of hypertensive subjects, or an incidence of 40 per cent. These authors, however, include all types of unilateral and bilateral disease, and since they offer no break-down it is impossible to evaluate even the approximate significance of this figure with respect to the relation between unilateral diseases and hypertension.

The fourth category of paper deals with the incidence of hypertension in pyelonephritis (Table IV). In 500 cases of pyelonephritis, Pearman, Thompson and Allen[35] found that only 9 per cent had hyper-

TABLE IV

INCIDENCE OF HYPERTENSION IN

Cases		*Per cent with Hypertension*
500	Pyelonephritis (unilateral & bilateral)	9.0
500	Goitre without hyperthyroidism	10 0
500	Gall-bladder disease	7.0

From Pearman, Thompson and Allen[15]

TABLE V

INCIDENCE OF HYPERTENSION IN UROLOGIC DISEASE

	Per cent with Hypertension
1. Friedman, Moschkowitz and Marrus[18]	
193 unilateral renal disease proven at operation	21.8
1006 living controls	22 8
2. Oppenheimer, Klemperer and Moschkowitz[21]	
79 necropsied patients with unilateral renal disease	27.5
333 control necropsies	24.0
3. Baggenstoss and Barker[20]	
97 necropsied patients with unilateral renal disease	29.3
100 control necropsies	29.0
4. Braasch, Walters and Hammer[27]	
1684 living patients with surgical uropathology	18.7
975 living controls	20.0
5. Crabtree and Chaset[16]	
150 nephrectomies for unilateral renal disease	9.0
(1981 living controls from 1 and 4)	21.4
(433 necropsy controls from 2 and 3)	26.5

tension, a figure that compares favorably with goitre without hyperthyroidism and with gall-bladder disease. This result is wholly incompatible with the belief that unilateral pyelonephritis tends to cause hypertension.

The last category of paper examines the incidence of hypertension in patients with demonstrated unilateral renal disease (Table V). Friedman, Moschkowitz and Marrus[18] found an incidence of hypertension of 21.8 per cent in 193 patients with unilateral renal disease proven at operation. This figure is lower than the 22.8 per cent incidence which

these authors found in a control series of 1006 living patients. Again Oppenheimer, Klemperer and Moschkowitz[21] found a 27.5 per cent incidence of hypertension in 79 necropsies where unilateral renal disease was demonstrated, a figure not significantly above the 24 per cent of hypertension which they found in 333 control necropsies. Baggenstoss and Barker[36] similarly found an identical incidence of hypertension in patients with and without unilateral renal disease, while Braasch, Walters and Hammer[37] found 18.7 per cent incidence of hypertension in 1684 living patients with surgical uropathology, a figure slightly less than in their 975 living controls. Lastly, Crabtree and Chaset[16] found only 9 per cent incidence of hypertension in 150 patients who had suffered nephrectomy for unilateral disease. Combining the living controls in 1 and 4 (Table V) the incidence of hypertension should have been 21.4 per cent, or considering the necropsy controls in 2 and 3, the incidence should have been 26.5 per cent. These figures are of the order of magnitude accepted by most medical statisticians as designating the incidence of hypertension in the adult population. Obviously, in Crabtree and Chaset's 150 patients, unilateral renal disease had exerted a very favorable influence on the frequency of high blood pressure!

The data summarized in this Table are impressive in their statistical demonstration that unilateral renal disease and surgical uropathology do not predispose to hypertension. Add to them the data from Pearman, Thompson and Allen in Table IV, with 9 per cent hypertension in 500 pyelonephritics, and the argument for renal origin appears tenuous indeed. The positive evidence on critical review boils down to seven cases in whom unilateral nephrectomy apparently effected a reduction in blood pressure and four cases in which a gross obstruction or compression of the renal circulation could have accounted for the hypertensive process, and we have in the recorded literature eleven cases in favor of the argument.

We conclude, therefore, that unilateral renal disease is rarely a cause of hypertension in man.

But how about bilateral renal disease? You will recall that it was Richard Bright[38,39] who first associated the elevation of blood pressure with kidney disease. He was impressed by the left ventricular hypertrophy of nephritis and allied diseases, and even in the absence of methods for measuring blood pressure, he deduced that there must be an increased load thrown upon the heart, and inferred that this load was

due to the resistance offered to blood flow by the kidneys. Later Johnson[40] and after him Gull and Sutton[41] demonstrated that in hypertension arterioles in other organs in the body were frequently narrowed as well, and then Allbutt[42] and Huchard[43] demonstrated that hypertension could exist in the absence of sclerosis of either the renal or systemic arterioles. From this observation, frequently confirmed, arose the conception that hypertension could exist in the absence of renal or systemic arteriolosclerosis, and consequently the aggregation of diseases formerly called "Bright's disease" was divided into those in which the kidneys were primarily involved, i.e., glomerulonephritis, polycystic renal disease and pyelonephritis, and those in which the kidneys were involved only secondarily to the hypertension. Hence the latter came to be called "essential hypertension." It seems to us that this division is still warranted.

But why does the blood pressure rise in glomerulonephritis, bilateral polycystic renal disease and bilateral pyelonephritis, if the kidneys are not primarily responsible for the pathological process in the large majority of patients with essential hypertension? The answer to this question can be identical with the answer which we have opposed to generalizing from the Goldblatt experiment: the kidneys can be the cause of elevated blood pressure where both organs are initially diseased, and in rare cases where only one kidney is affected, though whether the significant perturbation here is renal ischemia or some breakdown in renal metabolic activity cannot as yet be said; but the acceptance of this fact must not lead us into accepting the rare explanation for the general rule. The statistics are against it: hypertension has no higher incidence with unilateral renal disease than in the general population, and in the unilateral nephrectomies so far reported, in the opinion of the authors 50 per cent are improved, by our accounting only 10 per cent. In the nature of the problem, the true improvement is probably less.

It seems to us, therefore, that under the surgical and pathological evidence, as under the physiological evidence, the theory of primary renal origin is unproved. So far as the genesis of essential hypertension is concerned, the kidney appears to be the victim rather than the culprit. This is not to argue, however, that if the genesis is complex the kidney may not play an intermediary role, even as the pancreas may play a role in all perturbations of carbohydrate metabolism. But to ven-

ture in this direction is pure speculation. At this moment the origin of essential hypertension is unknown.

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SPECIAL ASPECTS OF THE PROBLEM OF THE RENAL ORIGIN OF HYPERTENSION*

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SINCE the time that hypertension could be produced with facility in animals by constriction of the renal arteries or compression of the renal parenchyma, the question has become pertinent whether essential hypertension in man also has its origin in the kidneys. It is obvious that gross obstruction to the renal blood flow and pressure on the parenchyma occur but rarely in human beings. But is gross obstruction or pressure necessary? If this is so, it is doubtful that the kidneys are responsible for most human hypertension, or that experimental renal hypertension has wide significance in clinical medicine.

The term "ischemia" of the kidneys has been so extensively employed that it has almost become synonymous with the term, "renal hypertension." Indeed, so little regard has been given to its definition, that one group of authors state: "By the term renal ischemia, we imply those changes which occur in the kidney following constriction of the renal artery with a Goldblatt clamp, be it actually ischemic, diminished pulse pressure, change in pulsatile flow or other factors." Clearly the term is well on the road to becoming meaningless. This is not necessary as the dictionary definition is clear: "local anemia due to mechanical obstruction to the blood supply."

It is the province of this communication to examine the evidence concerning three related problems: (a) whether experimental renal hypertension, human essential hypertension and hypertension induced by angiotonin are similar and hence study of one will lead to elucidation of the others; (b) whether "ischemia" in the sense of anemia of the renal tissue is the factor initiating and maintaining hypertension in experimental and human hypertension; (c) whether the so-called, "amine intoxication" theory of hypertension is consonant with the clinical and hemodynamic picture of experimental and human hypertension.

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Similarities of Experimental Nephrogenic Hypertension, Hypertension Elicited by Angiotonin and Human Essential and Malignant Hypertension

Justification for the great interest in experimental nephrogenic hypertension must ultimately come from the demonstration that it mimics essential and malignant hypertension in man. That a similarity exists has been apparent for some time, especially when due allowance was made for the anatomical and physiological differences between quadrupeds and man. This is perhaps most strikingly illustrated by the differences in psychic and somatic expressions of the nervous system during the disease. The aggressiveness and emotional instability of the typical human hypertensive are well known, but it is important to realize that the full blown disease may occur in their absence. Somatic expressions of hyperactivity of the nervous system usually consist of blushing, tachycardia, sweating, tenseness, etc., but these may or may not be present. It should cause no surprise that these varied manifestations are not found in hypertensive dogs, rabbits or rats. Furthermore, since these animals are quadrupeds the reduction in blood pressure which very often accompanies extensive sympathectomy in man is not seen. According to a view of Corcoran and Page[1] the benefits of sympathectomy do not depend on improvement of renal circulation but rather in part on denervation of the human reactive visceral splanchnic area, with resultant partial failure of venous return, most evident in the erect posture. Since dogs seldom stand erect, it is understandable that fall in blood pressure due to this mechanism would not occur in them. In addition, there is a vast difference in organization of canine and human nervous systems and this, too, must play some part in the results of sympathectomy. In some cases of human hypertension there is reason to suspect that the nervous system participates more actively than in others. In short, this is an example of the differences in signs and symptoms which might be anticipated from knowledge of the substrate on which the disease acts and from our beliefs as to its origin.

Despite these, in most cases, small differences, the similarities are great as will be clear from perusal of Table I. To my mind the most striking observation is that the hemodynamic picture is almost identical in both human beings and dogs and even the effects of the disease on the organism has some similarity.

TABLE I

COMPARISON OF EXPERIMENTAL RENAL HYPERTENSION, HUMAN ESSENTIAL HYPERTENSION AND HYPERTENSION INDUCED BY ANGIOTONIN

Experimental Hypertension.	*Human Essential Hypertension*	*Angiotonin Hypertension*
Heart		
Hypertrophy, left ventricular	Same	.....
Force—Increased	Increased	Increased
Work Efficiency—increased	Increased	Increased
Output—normal or reduced	Normal or reduced	Normal or reduced
Coronary sclerosis—not found	Common	Not known
Rate—normal	Normal	Normal or slowed
Pulmonary arterial pressure—normal	Normal	Increased in acute experiments
Venous pressure—normal	Normal	Often elevated in acute experiments
Kidneys		
Thickening of arteries—common	Common	Not known
Early morphological changes—none	None	Not known
Maximal ability to concentrate—reduced early	Reduced early	Not known
Glomerular filtration—maintained	Maintained	Maintained
Blood flow—normal or reduced	Normal or reduced	Reduced in acute experiments
Filtration fraction—elevated	Elevated	Elevated
Diodrast Tm—slowly reduced	Slowly reduced	Slightly reduced
Renin secretion—increased	Increased	.....
Unilateral renal disease—sometimes cured by nephrectomy	Same	.....
Liver		
α_2 globulin production—increased	Increased	Not known
Eyegrounds		
Arteriolar constriction, present	Present	Present
Arteriolar sclerosis, present	Present	Not known
Hemorrhages, exudates present	Present	Not known
Papilledema, present	Present	Not known
Retinal detachment, present	Present	Not known
Central Nervous System		
No evident change	Many somatic expressions of hyperactivity in some patients. Need be none.	None
Sympathectomy—no change in blood pressure	May reduce blood pressure	Does not affect response
Adrenalectomy—reduces arterial pressure	Probably reduces pressure	Reduces response only terminally
Hypophysectomy—reduces arterial pressure moderately	Possibly reduces pressure	No marked reduction in responsiveness
Thyroidectomy—no effect on pressure	No effect	.....
Pancreatectomy—no effect on pressure	Not known	No effect on responsiveness
Gonadectomy—no effect on pressure	No effect	No effect on responsiveness

Added to this is the fact that angiotonin, when injected into either animals or man, reproduces these hemodynamic changes with a reasonable degree of fidelity. Especially remarkable is the observation that it raises blood pressure asymptomatically and by narrowing the peripheral arterioles and increasing the force of the heartbeat the arterial pressure is raised, yet peripheral blood flow is not reduced. This is an unusual feat among the known pressor agents.

The evidence thus points clearly to the assumption that experimental renal and human hypertensives have much in common. Subsequent developments have suggested strongly that angiotonin has properties which are consonant with those which might be expected of a substance causing both experimental and human hypertension. The evidence is certainly not complete but enough has been accumulated to make me feel that it is angiotonin of renal origin, or something very similar to it, that mediates hypertension.

Is "Ischemia" of the Kidneys the Factor Initiating Hypertension?

It is understandable that following the demonstration of hypertension resulting from compression of the renal arteries, the assumption was made that it was a result of renal ischemia and reduced oxygen tension. The term, "ischemia," has been subsequently widely used and accepted as though proven by adequate evidence.[2] Indeed, some evidence supports this view, especially that demonstrating ischemic atrophy of the kidneys following clamping of the arteries (Goldblatt[2]) and reduction of blood flow distal to the clamp in the renal artery (Levy, Light and Blalock[3]). Goldblatt states that: "the changes in the tissues of animals with persistent hypertension and without signs of uremia were therefore abiotrophic rather than necrobiotic." "It is to those abiotrophic changes in the kidneys that the elevation of blood pressure is probably attributable because it is well known that in acute experiments clamping even of both renal vessels has little or no immediate effect on blood pressure."

Despite wide acceptance, the evidence supporting this view seems inadequate. Indeed, if ischemia of any significant degree were necessary for the production of hypertension, the methods now employed to elicit experimental hypertension would have little in common with the naturally occurring essential hypertension, for in the latter, evidence

of ischemia at times occurs only late in the disease. During the course of studies in dogs in which clamps were applied to the renal arteries or silk perinephritis induced, Corcoran and I[4] were early impressed by the fact that hypertension of marked degree resulted in animals in which there were no macroscopic or microscopic changes in the kidney tissue characteristic of ischemia. The problem, then, was not whether ischemia with hypertension could be produced by sufficient compression of the renal artery or parenchyma, but whether compression of a grade insufficient to produce ischemia resulted in hypertension.

Clearance methods were the most practical ones for measuring blood flow in the explanted kidneys of our dogs. In the initial phase of the work (Corcoran and Page[4, 5]) creatinine clearances were used as a measure of glomerular filtration and phenol red of renal plasma flow. It was shown that hypertension could be produced by clamping the renal artery without more than transient alterations in these clearances which suggested that neither renal blood flow nor intraglomerular pressure was decreased. Similar results have been obtained by Alpert and Thomas.[6] Later, inulin clearance (C_I) was used to measure glomerular filtration, and diodrast clearance (C_D) the effective tubular blood flow. The maximal ability of the tubules to secrete iodine from diodrast offered to them was used as a measure of the total amount of functioning tubular tissue, the so-called effective tubular mass or, briefly, Tm_D. The term, "tubular mass," refers to the amount of tubular cells which is able to secrete diodrast.

Using these more accurate methods, renal blood flow and relative intraglomerular pressure were again found normal in many dogs with hypertension induced by perinephritis or clamping the renal artery. Confirmation of these findings is found in the experiments of Friedman, Sugarman and Selzer[7] in which renal blood flow was not reduced when hypertension followed constriction of the aorta just above the mouths of the renal arteries.

Determination of diodrast clearance (C_D) in man with early hypertension shows that it often is reduced but *may* be normal, and the same is true of tubular mass (Tm_D). Thus the ratio C_D/Tm_D in most hypertensives will express the reduction in blood flow per unit of tubular mass; in short, ischemia of the tubules. The question remains to explain why some early hypertensives exhibit tubular ischemia and some do not. Blood flow in the kidney will depend at least on two opposing

forces, the resistance within the kidney itself and the mean systemic arterial pressure.[8] Most contemporary evidence (Corcoran and Page[8]) (Friedman, Selzer and Rosenblum[9]) suggests that resistance within the kidney early in hypertension is due in large measure to vasoconstriction produced by humoral agents. These agents elicit vasoconstriction of a very special kind, namely, constriction of the afferent and efferent glomerular arterioles, the small muscular arterioles just proximal and distal to the glomerular capillary tufts.

Constriction of the afferent arterioles will tend to damp the effects of the elevated systemic pressure and reduce intraglomerular pressure, whereas constriction of the efferent arterioles will tend to elevate intraglomerular pressure. The latter will be reflected in the filtration fraction from inulin clearance. Peritubular blood flow will tend to be reduced by the constriction of both and this will be reflected in reduction of diodrast clearance. Lamport[10] has recently presented a very interesting mathematical formulation of this viewpoint which aids in clarifying the many complex factors involved.

Actually in hypertensives the inulin clearance is slightly reduced or is normal. The cause of this slight reduction in filtration is not certainly known. It is probable that it results from some measure of constriction and possibly obstruction in the afferent vessels.

When the amount of glomerular filtration is considered in its relationship to tubular mass a different picture appears. Now its relative value per unit of functional tubular tissue (C_I/Tm_D) exceeds the mean normal value. In short, a relatively high filtration rate is being maintained in the kidneys of hypertensives, due, apparently, to increased systemic pressure and to efferent arteriolar constriction.

If resistance to blood flow in the kidneys increases, the systemic pressure may rise to oppose it and the actual blood flowing through them will be a balance struck between these forces. In short, as Corcoran and Page[8] found, the relative level of effective renal blood flow in hypertension is directly proportional to increased arterial pressure and inversely proportional to increased vascular resistance. It is not surprising, therefore, that the observed blood flow may be normal in some hypertensives and reduced in others. It follows that the finding of a normal rate of renal blood flow or a normal relationship between tubular mass and the blood flowing to it cannot be used as evidence against the participation of the kidneys in the genesis of hypertension.

As stated, the increased resistance within the kidneys seems to be mediated by substances in the blood. At present there is no *certainty* what these substances are but good evidence suggests the participation of angiotonin. The demonstration (Corcoran, Kohlstaedt and Page[11]) that angiotonin reproduces the intrarenal hemodynamic changes characteristic of hypertension adds weight to this belief, but does not prove it because a few other substances exhibit similar properties. As an isolated argument, the renal action of angiotonin can only place it among several substances which might be genetic factors in the development of hypertension.

While the evidence supporting the interpretation of clearance measurements is rapidly becoming stronger, there are reservations which must be clearly recognized. One of the most important of these is that reduction in diodrast clearance (C_D) may result from decreased effective renal blood flow *or* decreased extraction ratio, i.e., the ability of the tubular cells to extract diodrast presented to the cells by the blood, and at present there are no data to distinguish between these alternative explanations. There is no compelling evidence of decreased overall extraction of diodrast in the hypertensive's kidney. If, then, it is assumed that all of the diodrast is removed from the blood by the tubules as it is presented to them, then the diodrast clearance measures blood flow to the tubular tissue. The blood flowing to non-secreting tissue is not measured by this clearance; and hence, the relationship between total renal blood flow and flow to functional tubular tissue, in disease especially, is uncertain. Clearly, interpretation of the results of these methods must be made with the same care as Smith[12] and others have done. Nevertheless, they are the only ones capable, for instance, of determining the effectiveness of tubular cells damaged by scars, blockage and the other vicissitudes of disease.

In this connection, it may be pointed out that Goldring, Chasis, Ranges and Smith[13] are inclined to interpret the apparent lack of tubular ischemia in some hypertensives to the appearance in the kidneys of so-called "impotent nephrons." By impotent nephron they mean one in which the tubule remains anatomically intact and connected with an active glomerulus and a patent collecting duct despite the fact that it has lost its secretory activity, as tested by diodrast. Whether such impotent tubules lose all other tubular properties, such as capacity to reabsorb glucose, has not as yet been determined.[12] Since by definition, impotent

nephrons are unable to secrete diodrast they do not contribute to diodrast clearance (C_D) or tubular mass (Tm_D). The increased volume of blood per unit Tm_D which is made available for clearance by formation of impotent nephrons will appear in clearance measurements as apparent hyperemia of the residual functional tissue. Unlike the true hyperemia resulting from either dilatation of the renal arterioles or increased perfusion pressure, the blood may be deficient in some of its vital supportive qualities. Demonstration of the existence of impotent nephrons and of the inadequacy of blood from them to support normal tubular cells may prove to be an important aspect of renal physiology.

It is conceivable that reduced blood flow could occur to some tubules and not to others; a "patchy ischemia." But since there is no histological or other evidence of this and since it is not a necessary argument to describe the mechanism of the liberation of renin, proof of the existence of focal ischemia must await further observations.

We are now in a position to consider other evidence relating to the problem of intrarenal blood flow and pressure and its association with hypertension. Levy, Light and Blalock[3] found a decrease in blood pressure in the renal artery distal to the clamp, as well as decreased blood flow per gram of renal tissue when hypertension was present, suggesting that ischemia was necessary to the occurrence of hypertension. Despite decreased blood flow no anoxia could be demonstrated by determination of arterio-venous difference (Mason, Evers and Blalock[14]). Dock and Rytand[15] found the rate of flow of blood per gram of kidney tissue normal in rats with hypertension produced by subtotal nephrectomy. They indicate clearly that these hypertensive rats did not have renal ischemia.

Later experiments of Mason, Robinson and Blalock[16] show that the blood pressure distal to the clamp *may* return to normal, yet the hypertension persist. The pulse pressure, however, remains depressed.

The oxygen consumption of ischemic rabbits' kidneys was found to be reduced by Gerbi, Rubenstein and Goldblatt.[17] In general the degree of degeneration of the renal parenchyma was a fairly good indicator of the probable value of Qo_2, the lowest values corresponding to the most damaged kidneys. But diminution of tissue respiration occurred in some of their experiments without any histological changes. Mason, Robinson and Blalock,[16] on the contrary, found no change in respiratory activity in so far as this is indicated by the respiratory quotient and the

degree of aerobic glycolysis in kidneys of either hypertensive dogs or rabbits.

It is difficult to explain these completely discordant observations. Mason, Robinson and Blalock write that they repeated their experiments after the appearance of the paper by Gerbi, Rubenstein and Goldblatt, finding the results as before.

If low oxygen tension in the kidneys were part of the mechanism of renal hypertension, it might be anticipated that administration of high concentrations of oxygen would reduce the elevated blood pressure. Steiner, Weeks and Barach[18] have given pure oxygen to dogs with renal hypertension for 24 to 48 hours without observing any fall. Likewise three hypertensive patients did not respond with lowered blood pressure when they received the same treatment for three days. It is highly probable that any marked anoxia would be overcome by this treatment and if anoxia were part of the mechanism of hypertension, its abolition should reduce arterial pressure. Approached the other way, it might be anticipated that when the oxygen saturation of the blood is greatly reduced as often occurs clinically, arterial pressure should rise. It rarely does. Such experiments, of course, do not answer the question whether change in blood distribution within the kidneys themselves might not produce focal hypoxia.

Evidence of a different kind has been furnished by Kimmelstiel[19] and by Cox and Dock.[20] They estimated the capacity of the vascular bed of kidneys by perfusion after death, finding that in kidneys of most patients with hypertension but without uremia, it was within normal range. Blackman,[21] on the other hand, concluded from study of fixed tissues that narrowing of the renal arteries was usual. Cox and Dock consider his results erroneous and due merely to rigor and to the tissue fixation.

Several investigators (Fishberg;[22] Bell and Clawson;[23] and Williams and Harrison[24]) have observed many patients with hypertension in whom the changes in the renal vessels were of such slight degree as to furnish no adequate explanation for the genesis of the increased arterial pressure. Smithwick[25] has observed insignificant vascular changes in the vessels of biopsy specimens taken from the kidney during sympathectomy.

This evidence taken as a whole offers little support for the view that persistent reduction in blood flow and oxygen utilization occurs within the kidneys except when hypertension is of long duration and severe

secondary vascular change has supervened. For these reasons it seems doubtful if the oxygen tension within the kidney is reduced sufficiently early in hypertension to initiate some of the reactions leading to the formation of substances such as hydroxytyramine by anaerobic decarboxylation except late in the course of the disease. In the past year an array of theoretical papers have appeared in which the assumption is accepted as though it were a fact that hypertension is due to anoxia and ischemia of the kidneys.

What then are some of the factors which might initiate the liberation of humoral agents responsible for hypertension? Unfortunately, this problem has not been intensively studied. Kohlstaedt and Page[26] found in artificially perfused kidneys that reduction of blood flow without simultaneous reduction in pressure did not lead to liberation of renin but reduction of pulse pressure was shortly followed by its appearance in the renal vein. From these results it was suggested that reduction of pulse pressure is the initiating factor causing liberation of renin. What causes reduced pulse pressure we do not know, nor do we know why reduction in pulse pressure has this effect. Furthermore, artificial conditions had to be set up to perform such experiments. The changes in tissues occurring when the character of the pulsation is altered are known to be marked, but their precise nature is not known.

Amine Intoxication as a Cause of Hypertension

Various pressor amines have, from time to time, been suspected of causing essential hypertension but these suggestions never have been followed actively to ascertain the truth or falsity of the claim. For example, in 1935, Wolf and Heinsen[27] believed they had by crude methods demonstrated tyramine which originated in the kidneys in the blood of hypertensives. Paunz[28] found that long-continued infusion of tyramine caused morbid changes in the kidneys suggestive of nephrosclerosis. More recently, however, Enger and Lampas[29] were unable to find either hypertension or significant renal lesions in dogs given daily subcutaneous and intramuscular injections of tyramine (up to 300 mg.) for two and one-half years. Heinsen[30] investigated the question of the synthesis of tyramine by decarboxylation of tyrosine and concluded that pancreas alone could do this while spleen, kidney, liver, lung and muscle were unable to do so. Others found that tyramine was produced by the kidneys but Heinsen[30] after reinvestigation was still unable to

find it. Such studies as these carried little conviction.

But in 1937, Holtz[31] announced that kidney pulp could convert tyrosine into tyramine by decarboxylation. Later[32] it was shown that much more tyramine was found (or some pressor substance similar to it), if the reaction was allowed to progress under anaerobic conditions. In the presence of oxygen, amine-oxidases deaminized it to vaso-inactive aldehydes. This work has been the starting point for extensive investigations seeking to show that it is this or some similar mechanism which is responsible in whole or in part for hypertension.

Bing and Zucker[33] made the interesting observation that injection of dopa (1-dihydroxyphenylalanine) into the substance of a completely ischemic kidney converts part of it in two to four hours to a pressor substance with some of the properties of hydroxytyramine. Further, if dopa is injected into kidneys made partially ischemic by a Goldblatt clamp, a rise in blood pressure occurs. On the contrary, none occurs when the kidneys are normally perfused. No pressor substance is found when dopa is perfused through liver or gut. It was then found[34] that under anaerobic conditions ground guinea pig kidney forms hydroxytyramine actively, but if oxygen is admitted, its production is quickly reduced by one-half or more. Extracts of guinea pig, cat and human kidneys all produce pressor substance under anaerobic conditions.[35]

About the same time a series of articles appeared on the use of tyrosinase (a phenolic oxidase) in the treatment of experimental and human hypertension. The assumption was made that hypertension was due to the occurrence of mono- and dihydroxyphenolic amines such as hydroxytyramine and that tyrosinase or phenol oxidases would convert these to vaso-inactive quinones. Schroeder and Cohn[36] found that intravenous injection of tyrosinase consistently lowered blood pressure in hypertensive rats and dogs, but not in normal ones. This was confirmed in later work[37] and was extended to include human beings.[38] Schroeder has used mushrooms as the starting point for the preparation of his tyrosinase. Lately he writes[39] that an amine-oxidase prepared from hog liver is also very effective in lowering blood pressure in hypertensive dogs and rats. The inactivated enzyme did not affect the blood pressure, but this is denied by Prinzmetal, Alles, Margoles, Kayland and Davis.[40] Such evidence as this, if substantiated, would be strong evidence in favor of the amine theory of the pathogenesis of hypertension.

Other groups of workers at the Mt. Sinai Hospital have actively

concerned themselves with this problem. Soloway and Oster[41-43] showed that various aromatic amines are destroyed *in vitro* by aeration in the presence of quinones. They assume that the ischemic kidney is deficient in oxygen, hence its ability to destroy amines is deficient. This deficiency can be overcome by supplying an additional hydrogen acceptor. Hence, they injected intramuscularly o-cresol indophenol, a hydrogen acceptor and found a fall of 30 to 40 mm. Hg in arterial pressure of hypertensive rats but none in normal animals. Working on the theory that pressor amines could be inactivated by the ortho-quinoid intermediaries formed during the course of tyrosinase action, Friedman, Soloway, Marrus and Oppenheimer[44] treated hypertensive rats with a number of quinones. Four of them were found to lower blood pressure effectively with only slight local reactions and no thermal reactions. Some of the preparations were effective by mouth. Again the arterial pressure of normal rats was not affected.

Supporting evidence that both in animals and human beings with hypertension, defective renal deaminization may be present due to renal ischemia is presented by Oster and Sorkin.[45] In a series of five early hypertensives, intravenous injection of dopa produced a greater rise in arterial pressure than in five normotensives. The same procedure in hypertensive cats elevated blood pressure but not in normal ones or ones with acute renal ischemia. This is an extremely interesting observation and of sufficient importance to require very critical evaluation. Several obvious suggestions occur to mind: (1) the side effects such as nausea, vomiting, etc. which occurred frequently might well upset the results; (2) the early hypertensive has an especially labile blood pressure and hence the need for very exact control; (3) during the early phase of hypertension renal ischemia of any marked degree is unlikely to occur and since no measurements are given, the occurrence of "renal ischemia" remains conjectural; (4) only one reading of blood pressure is given before and one after injection of dopa; (5) the series is very small for the wide variation in the results. These suggestions are not given to disparage this work but point out that if the correctness of the work can be established, it would furnish a link in the evidence of genuine importance.

Evidence was found by Martin, Ichniowski, Wisansky and Ansbacher[46] that the oxidative destruction of adrenalin *in vitro* is promoted in a tyrosinase-adrenalin system by ortho-substituted phenols such as

catechol. Hence they administered tyrosinase along with catechol to a hypertensive dog and believed that the hypotensive effect was enhanced. This experiment had interesting possibilities but only one experiment is mentioned and the protocols of this not given, whether thanks to the authors or thanks to the editor.

It would certainly be premature at this time to attempt strict evaluation of the published results in this field. Many factors must be further investigated before a basis for sound judgment can be had. Already certain difficulties have appeared in the theory which may be hard to answer.

Amine-oxidase is absent from rats' kidneys[47, 48] as determined by studies of tissue respiration. This has been confirmed by a histochemical technique.[49] Decarboxylase is also lacking. Despite these facts, hypertension is easily elicited in rats by the usual methods. Certainly, then, the amine intoxication theory does not apply to all animals. It is especially to be regretted that the very animal on which most of the work has been done does not appear to have either amine-oxidase or decarboxylase in the kidneys.

According to Alles, Blohm and Saunders[50] the tissues of mammals do not normally contain any considerable amounts of tyrosinase or other phenol oxidases. The inactivation of phenolic amines is largely carried out by an esterifying process. They find the dissociation constants and the oxidation rates of tyrosinase-amine combinations such that this mechanism cannot account for any considerable part of the inactivation of tyramine of adrenalin in normal animals. According to them, it seems doubtful that the therapeutic effects of tyrosinase are due to its action as a phenol oxidase.

The evidence submitted by Brown and Maegraith shows[51] that the rate of oxidation by liver slices of tyramine is not reduced in hypertension experimentally produced. Tyramine evidently does not accumulate merely by not being destroyed.

There are certain other observations which must be considered in connection with the amine intoxication theory. Especially important among these is the type of vasoconstriction observed after administration of most pressor amines (Abell and Page[52]). The type characteristic of the hypertensive is one in which the peripheral arterioles are chiefly constricted with sufficient fall in the gradient of blood pressure that capillary pressure is normal. Further, blood flow is not appreciably

reduced. Compare this with the type of vasoconstriction which occurs when most vasopressor drugs are injected. For instance, Landis, Montgomery and Sparkman[53] found adrenalin, tyramine, pituitrin, guanidine, methyl guanidine, etc. elevate arterial pressure but always decrease skin temperature with varying degrees of vasoconstriction. In a word, there is disproportionate increase of peripheral resistance with decrease of blood flow, a circumstance which does *not* occur in the hypertensive.

A second point of importance is that most pressor amines increase cardiac output greatly. Yet the output in hypertensives is either normal or reduced. Taylor and Page[54] point out that tyramine increases stroke volume and greatly reduces heart rate, resulting in slight reduction in cardiac output, while angiotonin decreases stroke volume without much reduction of rate resulting in marked reduction of cardiac output. This is not the place for an extended discussion of the cardiodynamic effects of various pressor substances. Suffice it to say that the effects of tyramine and most other amines are such as to make it unlikely that they participate in the genesis of renal hypertension.

Most pressor amines when injected into human beings cause symptoms and signs of a most disagreeable nature. Nausea, vomiting, sense of oppression, sweating, tachycardia or bradycardia, prolonged headaches, increased peristalsis of the intestine, increased metabolic rate, shortened circulation and mydriasis are usual. These are signs and symptoms seldom seen in patients with essential hypertension or dogs with experimental hypertension. However, they do occur in cases of hypertension due to liberation of the pressor amine, adrenalin, in cases of pheochromocytoma of the adrenal glands.

Whether anaerobiosis is sufficiently intense in the kidneys of hypertensives to initiate the decarboxylating mechanism seems doubtful. Most evidence gathered so far is against the view that it is. Possibly late in the disease when renal blood flow is seriously compromised, sufficient hypoxia may exist. Thus, in summary, it may be said that the theory of amine intoxication has some interesting experimental work substantiating it but also many important objections to it.

Summary

The evidence concerning the following three questions has been examined: (1) Whether experimental renal hypertension, human essential hypertension and hypertension induced by angiotonin are similar

and hence study of one will lead to elucidation of the others? It was concluded that allowing for differences in organization of quadruped and man, the similarities especially as regards hemodynamics are great. (2) Whether "ischemia" in the sense of anemia of the renal tissue is the factor initiating and maintaining hypertension? It was concluded that it was not a necessary factor and that the wide use of the term is unjustified by the evidence. (3) Whether the so-called, "amine intoxication" theory of hypertension is consonant with the clinical and hemodynamic picture of experimental and human hypertension. It was concluded that while interesting and important evidence has been presented, there are many serious difficulties that have not been explained which, on the whole, militate against its playing an important part at least early in the course of the disease.

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THE MANAGEMENT OF PERIPHERAL VASCULAR DISEASE*

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INTRODUCTION

HERE, as in all fields of medicine, we are bound by fixed ideas as to underlying pathological processes and what is perhaps more serious by set patterns of therapy. Despite the fact that well known and reliable investigators still disagree as to the processes which produce atheromatous changes in the arteries, most of us have formulated a picture of these changes that is all too final in our minds and having formulated such an opinion we are wont to treat the patient with obliterating arteriosclerosis with a routine much too fixed to be effectual in every case. Too frequently the diagnostic terms themselves immediately center our therapeutic tendencies on an ineffectual method. As only certain cases of pulmonary tuberculosis should receive pneumothorax—only certain patients with phlebitis may need chemotherapy or anticoagulants. It therefore behooves us to evaluate the organic changes present in any one condition and likewise determine what associated functional disturbance should be treated. Every woman whose hands and feet show vasomotor changes is not suffering from a Raynaud's syndrome. I shall therefore this afternoon devote my discussion to general pathologic processes involving the peripheral vascular system and their management. In order to conform to present day concepts of disease we must use names to describe the various processes encountered, but I hope to impress on your minds that a name so commonly used as arteriosclerosis actually covers a great variety of processes in the arteries, only a very small percentage ever leading to gangrene or amputation.

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CHART I

PROCESSES REDUCING ARTERIAL SUPPLY
WITH ASSOCIATED SYMPTOMS

Process	*Rate of Development*	*Symptoms and Signs*
1. FUNCTIONAL		
a. Complete Spasm	Sudden	Coldness, numbness, pain, pallor, gangrene
b. Recurrent Spasm	Gradual or varying in degree	Pallor, cyanosis alternating with rubor, coldness, superficial ulcerations
2. ORGANIC		
a. Embolism	Sudden	Coldness, numbness, pain, gangrene
b. Thrombosis Sclerosis Medial or Intimal	Gradual	Intermittent claudication, coldness, rest-pain, ulceration, gangrene
Thrombo-angiitis obliterans	Rapid	Same as with embolism.

Note: Most organic occlusive processes are associated with functional disturbances

ARTERIAL DISEASES

When pathological processes involve the arteries and arterioles we have as a result alterations in blood supply to the part of the body supplied by these vessels. As a result of this alteration in supply the patient comes to us with certain symptoms.

If the supply is increased above the average, as it rarely is, we have a feeling of swelling, increased warmth and various paresthesias especially burning and throbbing. Erythromelalgia is about our only example of such a disease and is a rare condition. Since Weir Mitchell[1] described it as a neurological problem, no effective therapy has been found to relieve its distressing symptoms. One would expect that drugs working through the autonomic nervous system to produce arterial spasm would be therapeutically useful, but the annoying and serious side effects of such therapy have eliminated their value. If the supply is decreased we find a great variety of symptoms depending on many variable factors (Chart I).

It is therefore evident that there are many variables present in con-

CHART II

EVALUATION OF THE PROCESSES REDUCING ARTERIAL SUPPLY

1. Degree of spasm in the main and collateral vessels.
2. Rapidity of development of the process.
3. Type of process as it manifests itself in the wall of the vessel (Rule out blood dyscrasias).
4. Extent of involvement of the process: Locally and generally.
5. Association with other processes, such as phlebitis.

ditions which reduce blood flow through the arterial tree to an extremity. In addition to those enumerated in Chart I, one must consider the effect of alterations in cardiac output, as many individuals suffering from peripheral vascular disease also have associated heart disease. A failing heart will often allow sudden and serious arterial thrombosis to occur in peripheral arteries whose walls are already damaged. Before instituting treatment sufficient time must be spent to evaluate in each patient with reduced arterial supply the factors enumerated in Chart II.

This paper cannot cover all of the various diagnostic procedures and tests to help one determine these facts. You are, therefore, referred to the vast amount of literature on this subject, and should familiarize yourself with the pertinent facts to be obtained by physical examination, oscillometry, x-ray studies with and without contrast media in the arteries, temperature studies, ergometer studies and circulation time tests.

TREATMENT

Certain basic and almost self-evident features of treatment are applicable to all patients suffering from reduced arterial supply (Chart III).

Let me stress this first factor of rest. Since practically all patients in this group have varying degrees of spasm as a factor in reducing the blood flow, nervous tension must be eliminated as far as possible. It is not uncommon for me to have an intelligent business man come into my office complaining of intermittent claudication of a mild degree, but unduly alarmed by previous consultations as to the possibility of losing his leg. After a careful examination and reassurance he may report back a few days later for tests and, before treatment has been outlined, state

CHART III

PRINCIPLES OF TREATMENT

1. Rest
   a. Mental
   b. Physical
2. Optimum position of the extremity
3. Optimum environmental temperature
4. Elimination of factors reducing blood flow
5. Use of agents to increase blood flow
   a. Reflex dilatation
   b. Drugs
   c. Hormones
   d. Mechanical
   e. Alterations in blood viscosity and volume
   f. Foreign protein
6. Surgical procedures

that he can walk further and that his leg feels better. With reassurance his vasospasm associated with worry has become less.

Not only must we rest the mind, but we must not overtax the muscle or muscles with impaired nutrition. Where symptoms are early and reduction in blood flow is moderate, simple advice as to the amount of muscular activity is sufficient. Never let these patients force themselves against pain due to muscle ischemia.

In the more advanced cases where pain is present with rest or excessive emotion or cold, complete rest is just as important as it is in advanced pulmonary tuberculosis. The man with night pain or early gangrene needs weeks or months of complete freedom from use of the involved extremities and removal from the exciting causes of decreased blood flow when known. Any attempt to arbitrate this rule nearly always offsets the value of other treatment.

It is therefore apparent that it takes careful and intelligent handling of the individual to accomplish this rest without increasing the tension due to economic worries. Again, one of the problems of geriatrics rears its head unsolved.

Second: What is the optimum or ideal level at which to place the extremity with impaired arterial supply? Elevated, dependent or at heart level? There is no set rule. Here again a clear analysis of the problem is necessary. Let us take a theoretical case. Suppose we have a man with

obliterating arteriosclerosis and gangrene of the first toe. He has hypertension and his lesions are most marked peripherally. In his case the foot at heart level will probably receive the maximum supply of blood. If he has normal arterial pressure or hypotension, elevation of the head of the bed four to six inches will permit gravity to aid in supplying blood to the toes; but if he has large varicose veins, these will fill and prevent return of blood and stasis will result. This patient may be better off with a slight elevation of the foot of the bed.

Third: The proper environmental temperature for any given case is of utmost importance. It should be unnecessary for me to emphasize that extremities with impaired arterial supply are more easily frozen or burned than those with structurally and functionally normal arteries. All too frequently we see patients with burns of a serious degree following the unwise application of heat to the involved extremities. It is only natural when a patient has a cold extremity to warm it. However, if one applies heat by contact, radiation (infra-red) or by electrical energy (short wave or diathermy) serious results often follow. The leg with impaired blood supply is usually less sensitive to the recognition of excess heat. An infra-red lamp may blister or short wave may produce a deep burn before the patient is aware of it. Therefore, the only safe rule to follow is to avoid applying to the involved part direct heat greater than body heat. For most cases of arterial impairment, a cradle with a thermostatically controlled source of heat to maintain a temperature of 88° to 92° F. will produce the maximum circulation with the greatest degree of comfort.

Let us consider for a moment what happens when the temperature of an extremity is elevated by environmental heat. The metabolic rate of the tissues varies directly in proportion to the temperature. In other words, when the temperature is elevated metabolism increases and more blood is necessary. If the arterial supply is so damaged that the added demand cannot be met, pain increases and death of tissues may follow. Therefore, it follows that tissues supplied with badly damaged arteries should be kept at lower temperatures than those with better circulation.

Recently it has been found that if the air in the cradle surrounding a limb with an acute arterial shut-off, due to an embolism, is kept at low temperatures of 50° to 60° F, there will be less danger of gangrene and pain will be less marked. This can be accomplished by packing ice bags around the cradle and if necessary using a small fan to keep the cooled

CHART IV

FACTORS REDUCING BLOOD FLOW

1. Tight garters
2. Tight bandages
3. Tight shoes with rough interiors
4. Tight shirts and sweaters
5. Bad postures in occupations—leg over ladder rung—kneeling for long periods, etc.
6. Standing in one position for a long time
7. Repeated shocks or vibratory trauma
8. Tobacco and ergot

air moving over the leg. While this is being done vasodilatation can be accomplished by drugs and by reflex methods to be described later and the cardiac function improved. This type of therapy does not apply to thrombi lodging high in the thighs or in the iliac vessels where immediate embolectomy is indicated whenever possible. In summary, then, one might say that the more complete and sudden shut-offs need lower environmental temperatures than do the gradual incomplete closures.

Fourth: If in the management of peripheral arterial impairment problems it is our aim to increase blood supply, then one should carefully eliminate all factors which tend to diminish arterial supply. Some of these seem so self evident that I would hesitate to mention them except for the fact that I see referred patients frequently to whom such advice has been overlooked. It is not necessary more than to enumerate most of them (Chart IV).

Although ten years have passed since Maddock and Coller[2] demonstrated the vasospastic effect of smoking and although their work has been confirmed by numerous workers including members of our own clinic staff,[3] many physicians are not being emphatic enough with their patients suffering from occlusive arterial diseases regarding the use of tobacco. I believe that all workers in this field are firmly convinced that tobacco is a powerful vasoconstrictor and that it must be eliminated completely from the habits of persons suffering from impaired blood supply due to arterial (and even venous) disease. Reduction in amount is not

adequate. The use of filters does not eliminate enough of the vasospastic factors and the so-called denicotinized cigarettes still produce a high degree of spasm. Cigar and pipe smoking is apparently as serious as cigarette smoking.

Although not directly associated with producing further impairment of circulation these individuals should be warned against trauma, cutting nails too close and the use of necrotizing salves and ointments containing salicylic acid, carbolic acid and iodine. Fungus infections should be treated by soaks of non-irritating substances like potassium permanganate 1:4000 or 1:8000 at body temperature.

Again, let us look at the patient as a whole especially as to the cardiovascular system. If there is heart involvement, if the patient is overweight, if he has other debilitating disease, treat these problems along with those in the extremities.

Fifth: I have left the most dramatic angle of therapy and the one we usually think of first as the final problem of discussion under the management of reduced arterial supply. What means have we available to increase blood flow where the damage is for the most part localized to an extremity? Methods effectual in overcoming spasm are of little value in obtaining more blood through vessels with narrowed lumens due to disease of their walls. So again let me emphasize the importance of evaluating the process. Where spasm predominates, vasodilating mechanisms are indicated. Reflex methods of vasodilatation are of great help. By heating the upper extremities in hot baths or by applying electric pads to the back and abdomen, or by using diathermy or short wave to the trunk to increase body temperature, peripheral vessels in spasm in the involved lower extremity are reflexly opened and the blood supply increased.

Drugs (Chart V) have relatively little value in producing vasodilatation of the blood vessels in an extremity. The nitrites and the purine derivatives either have no demonstrable effect or their systemic effect is so marked that a drop in blood pressure offsets any beneficial effect. Recently papavarine in large doses of 1 and 1½ grs. has been reported by Elek and Katz[4] as effectual in producing vasodilatation in peripheral vascular disease. In a personal communication from Dr. Mulinos[5] of the College of Physicians and Surgeons of Columbia University I have been informed that the spasm of Raynaud's syndrome could be overcome with this drug.

CHART V

DRUGS USED IN THE TREATMENT OF ARTERIAL DISEASES

Drug	*Action*
Iodides	On cholesterol metabolism?
Arsenic Bismuth	On syphilis
Sulfonamides	On infections
$KMnO_4$	Fungicide
Opiates	To relieve pain and spasm (reflexly)
Salicylates	To relieve pain and spasm
Xanthanes	To relieve spasm
Nitrites	To relieve spasm
Alcohol	To relieve spasm
Histamine Cholines	To relieve spasm
Adrenalin Ephedrine	To increase tone
Phenylhydrazine	To reduce the red blood count

Drugs which relieve pain of peripheral arterial insufficiency may be of value in increasing circulation by eliminating reflex spasm. Pantopan and the salicylates are useful in this sense. Combinations of vasodilating drugs and sedatives have even greater effect than either alone.

Whiskey in small amounts often causes a slight dulling of pain and probably some slight vasodilatation. However, in sufficient quantities to produce signs of intoxication, a reduction in blood flow to an extremity has been demonstrated by Veal.[6]

Hormones have been tested for several years to determine their status in producing vasodilatation.

Thyroid extract increases blood flow but also increases body metabolism and its use is of questionable value.

Very little work has been done on pituitary extracts and none are known to be of value.

The androgens and estrogens* have been reported by various workers to increase coronary and possibly peripheral blood flow. Whether

* Supplied to us by Ciba & Company for experimental work (Diovycylin and Perandron).

this effect is a result of a direct action on the peripheral vessels or an indirect one by overcoming tenseness in the nervous system is still undecided.

Certain tissue extracts promise even more efficient hormonal activity. Although pancreatic extracts have been available for nearly ten years there is still much disagreement as to their value and what is more as to their mode of action. We have had considerable experience in the Vascular Clinic of the New York Post-Graduate Hospital with several of these preparations. There is one significant observation borne out by clinical tests. Intermittent claudication associated with occlusive arterial disease is definitely benefited by their use. Walking distance is increased in some instances by considerable amounts. Recent articles by Fatherree and Hurst,[7] Klein, Saland and Zurrow[8] substantiate this observation. However, there is so far little evidence to support their value in the relief of rest-pain or in the healing of gangrenous lesions.

In animal work a direct effect on blood pressure can be demonstrated suggesting vasodilatation. One product* is standardized by noting its effect on the blood pressure of the dog. One unit of this material will depress the systolic blood pressure to the same degree that 1 mgm. of adrenalin will elevate it in the same animal. Unfortunately, all of these substances have to be administered hypodermically. The usual dose is 3 cc. intramuscularly three times a week. The patient can be taught to give the injections as easily as one would give insulin. We have seen many patients, in whom intermittent claudication is the predominant symptom, able to do much more work while using this form of therapy.

Cholines may be considered as hormones and again we have had extensive experience with their use. There are many forms available for therapy. Acetyl choline is mild in its action while Acetyl B methyl choline hydrochloride** is about 100 times more potent. They are of little value when taken orally and when given hypodermically produce such marked vasodilatation that vasomotor collapse may result. Some years ago we therefore developed a method of applying them locally by galvanic current (iontophoresis) in the treatment of vasospastic diseases affecting especially the skin. They are of real value in healing superficial ulcers due to impaired arterial supply and associated arteriolar spasm.

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* Depropanex supplied to us for experimental purposes by Sharpe & Dohme.
** Supplied to us by Merck & Company since 1935 for experimental purposes.

Examples of such pathology are ulcers associated with varicose veins and in some cases ulcers associated with arteriosclerosis. Recently we have treated a few patients by simply spraying a 1/5 per cent solution onto the ulcer with satisfactory results until the ulcer is about healed. It would appear that the galvanic current is necessary to cause absorption of the drug through the unbroken skin. For the technique of iontophoresis I would refer you to a paper by Kovacs.[9]

Mechanical methods of increasing blood flow have flooded the medical apparatus market. Since Buerger[10] described his method of postural exercises, various means have been devised to apply this principle. Most of these are accomplished by active effort on the part of the patient and when the blood supply is not too impaired such an application of the method is wise. However, where the exertion necessary to carry out the exercises increases the pain a passive method is indicated. Several types of apparatus have been developed to accomplish this but the most satisfactory one from our experience is the oscillating bed of Sanders. This permits drainage and filling of peripheral leg vessels by gravity without effort on the part of the patient and over long periods of time even to twenty-four hours a day. Through adjustments the rate of the cycle and the degree of dependency and elevation of the foot can be altered. Such adjustment to meet each patient's needs is extremely important. The foot should be in the elevated position long enough and high enough to produce slight pallor only and in the dependent position to produce slight rubor. A faulty adjustment which tends to decrease the amount of blood supply by keeping the leg elevated for too long a period may actually cause more pain and a progression of a vascular lesion.

Since such a therapeutic method has little effect on spasm, it should be used together with a heat cradle set for an optimum temperature, reflex vasodilating methods and drugs in order to obtain maximum blood flow.

Intermittent venous occlusion, as described by Collens and Wilensky[11] and by Linton,[12] is based on the principle that there is a reflex dilatation and increased blood flow in the arterial system as a result of this intermittent interference with the venous return. This method would therefore be of value only where vasospasm is a major factor and would be of little help where organic changes predominate. There is still considerable controversy as to its value as a mechanical form of therapy.

The same may be said for the "boot" in which an involved extremity is placed and the pressures in the boot are alternately increased and decreased above and below atmospheric level. Here again such pressure changes should be just sufficient to produce pallor and rubor and the period of pallor should not be too long. The cuff which maintains the pressure and which fits around the thigh or arm must be tight enough to avoid the leakage of air but not so tight as to obstruct venous return. Moreover, in many instances collateral blood flow is located near the surface of the extremity and a poorly applied cuff may interfere with this supply.

Recently we have been experimenting with a vibrating table in which there are alternate long and short vibrations with the extremity so placed that the dynamic effect would force blood peripherally. The method is simple and is easily applied but it is still too new to report on its effect. In persons with a sensitive sympathetic nervous system a reflex spasm from the vibrating factor may offset its value.

Before leaving the discussion of mechanical aids I would like to stress the point that most patients suffering from arterial disease can be successfully treated without the use of such methods. Moreover, when they are used they must be thoroughly understood and each patient must be studied while receiving such treatment to be sure that the therapy is of value and, what is more important, that the apparatus is properly *applied* and *adjusted*.

Various investigators have attempted to treat occlusive and vasospastic arterial problems by attempting to alter the blood volume or viscosity. One of the earliest forms of such therapy was the instillation of large amounts of Ringer's solution by duodenal tube. This method naturally had many undesirable side-effects. Later Bernheim[13] suggested the use of 250 cc. of 2 per cent sodium citrate solution in an attempt to reduce blood viscosity and, more recently, Theis and Freeland[14] have been using sodium tetrathionate. All such methods are helpful but for the most part necessitate intravenous therapy which is expensive and time-consuming and which may be complicated by reactions if one is not careful in administering these infusions.

The same objection may be brought forward regarding the use of hypertonic saline solution of 3 per cent or 5 per cent and of 300 to 500 cc. volume. Although such intravenous therapy has been shown to increase blood flow into an extremity and lead to healing, especially in

thromboangiitis obliterans, I feel that simpler methods can accomplish the same result.

An example of a simpler method for producing vasodilatation is demonstrated by foreign protein reaction. Intravenous injections of carefully measured doses of plain typhoid vaccine, starting with 3 to 5 million organisms will produce vasodilatation lasting 12 to 36 or even 48 hours. Sulphur in oil or milk given intramuscularly will produce the same result but the dose is hard to regulate and the pain produced makes the use of these reagents unsatisfactory. When intravenous typhoid vaccine is used the dose can be repeated every 72 to 96 hours increasing it gradually to give a slight temperature reaction but without chill.

Sixth: I shall not attempt to deal at length with the surgical procedures of value in the management of arterial diseases. Pratt[15] recently read a paper on this subject before this group.

Amputation will usually be avoided by the careful management of a patient as above outlined. However, when it becomes apparent that it is necessary, do not delay. Choose your site so that secondary amputation will not be needed and prepare your patient to avoid shock and thereby perhaps precipitate a sudden closure and gangrene in another extremity.

Interference with the sympathetic supply by novocaine or procain injections of the nerve roots supplying the affected extremity will often give maximum vasodilatation for a period long enough to turn the tide from a progressing lesion to an arrested one. Furthermore, severance of peripheral sensory nerves will relieve pain and its reflex vasospasm and cutting of the sympathetics will give permanent vasodilatation and is the surgical procedure of choice where a chronic vasospastic major factor is the problem to be overcome and where other forms of less radical therapy have failed. A typical example of such a problem is a severe Raynaud's syndrome.

In a discussion on the management of peripheral vascular diseases one cannot conclude his remarks without spending a few minutes on the anticoagulants. Since Murray and Best[16] described heparin and Link and his co-workers[17] dicoumarin, a great deal of work has been done with these substances. Previous to these discoveries leeches and extract from leeches had shown some value as anticoagulants.

In arterial disease the problem confronts us as to when to turn to these potent agents. Since heparin exerts its effect rapidly and dicoumarin, which is usually given orally, takes 24 to 48 hours to produce a

delay in coagulation, one can be guided in his selection of reagents by these facts. Therefore, in embolic problems with the danger of superimposed ascending thrombosis and in arterial surgery heparin must be used, since in 48 hours fatal thrombosis may have occurred. However, in chronic diseases such as thromboangiitis obliterans with a thrombotic problem, dicoumarin is preferable. As we understand the action of these substances we may find that a combination of the two may be most satisfactory, starting with heparin to get its immediate effect and following it with dicoumarin to conclude the course of anticoagulant therapy. Heparin is expensive at present, has to be given by continuous infusion, which is annoying to the patient, and its effect must be watched by frequent coagulation time tests. Dicoumarin on the other hand is cheap, can be given by mouth and the alterations in the prothrombin and coagulation times are less rapid and therefore tests for these functions on the blood do not have to be carried out as frequently. However, when heparin is discontinued its effect is over in a few hours while dicoumarin maintains an increase in the coagulation time for days. Transfusions of whole blood will however stop the anticoagulant effect of dicoumarin if the coagulation or prothrombin times become too prolonged. Banked blood loses its thrombokinase and is therefore of no value in stopping the action of dicoumarin.

Until such time that these substances are better known, especially dicoumarin, I believe the average physician, inexperienced with their use, should have guidance in treating a patient with them. Excessive bleeding, especially renal in origin, may occur if too great a dosage is used.

In addition to the problems mentioned, the anticoagulants may prove of real value in preventing mural thrombosis in coronary disease, in limiting thrombotic lesions in vegetative endocarditis and thereby reducing the possibility of pulmonary or peripheral embolism. Wright and Prandoni[18] have demonstrated the value of dicoumarin in the treatment of thrombophlebitis.

Management of Venous Problems

Venous pathology of the extremities is chiefly on an organic basis. Although the veins have the power to dilate and contract, this function is perhaps less important than it is in the arterial side of the circulation. The main problems confronting us are shown in Chart VI.

CHART VI
DISEASES OF THE VENOUS SYSTEM

I. Varicose veins
   a. Congenital
   b. Acquired

II. Distended—pulsating veins
   a. Due to arterio-venous anastomosis
   b. Due to tricuspid insufficiency

III. Phlebitis
   a. Acute
   b. Chronic
   c. Migratory

IV. Thrombosis
   a. Primary
   b. Secondary

Varicose veins when definitely developed are a problem for surgical procedures. Only minor vessels can be successfully eradicated by local injection therapy. Unfortunately, many patients have received repeated injections of various sclerosing solutions into large vessels with little or temporary relief. It has been demonstrated that many of the thrombotic lesions produced by local injections are absorbed within a few months and the veins are as varicose as previous to therapy; sometimes, even more so.

It is therefore evident that in all cases of varicosities of even moderate degree, and especially in those in which the saphenous vein is distended by back flow from the femoral vein, surgical ligation with resection and retrograde injection is the procedure of choice. In addition to the above procedures, all incompetent communicating vessels from the groin to the lower leg must likewise be ligated to prevent the future development of local venous distention and varicosities at such sites. Again I leave the description of the technique to the surgeon.

The general practitioner and the internist must, however, be able to select those patients whose therapy is surgical. He must be familiar with the tests to demonstrate back flow through superficial veins such as the Trendelenberg test and its modifications. It is of the utmost importance that he test his patient for competent deep vein function. The Perthes test is easily and simply performed and in 15 to 20 minutes one can determine the patency of the deep veins. The leg is bandaged from the ankle to the groin with an elastic type of bandage applied tight enough

to obliterate superficial veins and still permit arterial pulsations to be obtained at the foot. The patient should be able to walk for 15 minutes without cyanosis of the foot or pain anywhere in the leg. Either of these signs or symptoms is a contraindication to obliteration of the saphenous system.

One is likewise frequently confronted by the problem of complicating arteriosclerosis. It has been our experience that in ambulatory patients the obliteration of the veins is beneficial. However, in patients with arterial lesions so advanced that gangrene is present or imminent, venous back-pressure is usually not a factor as, with bed rest, drainage is usually adequate. However, if these patients develop collateral arterial circulation and become ambulatory, then removal of the venous pools becomes necessary.

All patients with varicose vein problems must be studied carefully to rule out diabetes and, if present, it must be controlled before surgery is undertaken. The same holds true for syphilis.

The question also arises as to the wisdom of operating on varicose veins complicated by phlebitis. Certainly the best rule to follow is to avoid surgery until evidence is obtained that any such process has subsided. The erythrocytic sedimentation test is a helpful guide in determining activity of phlebitis.

There has been a tendency in recent years to ligate the femoral vein in certain cases of deep phlebitis. In reviewing a series of cases in which this was done and comparing the results with less radical therapy, I could find no decrease in the incidence of pulmonary emboli or quicker recovery from the phlebitis. Moreover, there is the definite possibility of some permanent edema because of this procedure.

A few words must be directed at an unusual but interesting phenomenon, that is, pulsating veins. In any patient with distended veins, always watch for pulsations. In making this observation elevate the extremity above heart level. In so doing varicose veins should collapse, while vessels filled with arterial blood remain distended. The stethoscope frequently will locate the anastomosis between the artery and vein with the revealing of a bruit. In rare instances the veins of one or both lower extremities will pulsate with back flow from a tricuspid insufficiency.

Phlebitis is one of the problems of peripheral vascular disease which is usually easily diagnosed but is frequently exceedingly resistant to therapy.

It may be unnecessary repetition but the prophylaxis of phlebitis is really of greater importance than its treatment. In every surgical procedure every possible means should be used to maintain rapid and full blood flow through the extremities, especially the lower ones. We have only time to enumerate such means. The patient should be made to breathe deeply on return from the operating table, either by the use of CO_2 inhalation or by injections of coramine. Tight constricting bandages must be avoided and the extremities must be kept warm. If there is question of shock, elevation of the foot of the bed is imperative and the replacement of blood volume with plasma or blood is urgent. In healthy individuals presurgical thyroid medication will speed up blood flow and in patients with cardiac disease adequate therapy directed at poor cardiac output must be given. Anticoagulant therapy in individuals with a history of previous embolic accidents or phlebitis may in the future be a routine postoperative procedure.

When we are faced with the treatment of phlebitis itself, certain principles of therapy must be carried out. Again, we do not have time to discuss in detail each principle. However, this paper would not be complete without some time on this important problem.

Many of the principles of prophylaxis may be applied to the treatment of the active process. Since the etiology of phlebitis is still confused and the processes not clearly understod, many of our present forms of therapy may be discarded in the future. However, at present the following procedures seem to promote the most rapid healing.

1. Use all means to promote rapid blood flow through the involved extremity, such as hot packs for 18 to 24 hours a day, vasodilating procedures, especially paravertebral nerve-block, elevation of the extremity and the use of thyroid by mouth. Although I personally am not in favor of tight bandaging and active exercise, such as walking, some workers advocate this.

2. Removal of foci of infection, especially fungus infections.

3. The treatment of the infection itself by chemotherapeutic drugs such as the sulfonamides and arsenicals and bismuth.

4. The use of anticoagulants such as heparin and dicoumarin. This form of therapy is certainly indicated in those patients prone to throw off emboli or in those in whom the thrombotic lesions predominate. Again, I suggest you turn to the paper of Wright and Prandoni published in the Academy Bulletin last year for the details of such therapy.

Before leaving the problem of phlebitis let me discuss briefly the annoying symptom of neuritis that frequently accompanies this process. Since we know that the pathological process frequently involves the perivascular tissues, it is evident that in healing, the sensory nerves accompanying the vessels may become irritated and pain may result. Many patients still have considerable pain along the course of the veins long after the acute process has subsided. When one is convinced that activity of the process no longer exists, then massage, baths and active exercises are indicated. Extra vitamin "B" in the entire complex may be of real value during the active and arrested stages of the disease.

Finally, a word or two about non-inflammatory venous thrombosis. This is usually secondary to some chronic pressure or perhaps to an invading new growth, although one occasionally sees a patient with thrombi developing in various parts of the venous system without evident cause. The treatment of such problems is naturally first to remove the cause, if known, and secondly to increase blood flow by the means used in the treatment of phlebitis.

Diseases of the Lymphatics

Of the three vascular systems in the extremities we probably know less about the lymphatics than we do of the arterial and venous channels. There is a superficial and a deep system of lymphatic vessels in the legs but unlike the veins they do not communicate except through the popliteal and inguinal areas. All of the lymphatic drainage from the leg, superficial and deep, joins below Poupart's ligament and runs closely to the veins, even being enclosed in a tough fibrous sheath beside the vessels.

In the upper extremity, the lymph drainage system is more complicated, but all vessels drain through the axillary lymph nodes. As in the venous system, obstruction to a large vessel is followed by drainage through collateral vessels. If the cut ends of a severed vessel are approximated, regeneration takes place and the vessel resumes function. The regeneration of the vessels is rapid. An incision is bridged in four days and by the eighth day regeneration is adequate to carry lymph.

The flow of lymph through these channels is controlled principally by muscle contraction. Valves in the system keep the flow moving proximally. Flow is fairly rapid under normal circumstances and probably takes only a minute or so to pass from the foot to the larger vessels in

the abdominal cavity. Lymph clots more slowly than blood (normally in 10-20 minutes) due to a deficiency in thromboplastic substances.

The diseases affecting these channels may be divided into two main groups; first, inflammatory and second, obstructive. This second group may be the result of congenital defects, pressure on, or destruction of the lymphatics, or due to chronic infection.

Acute lymphangitis usually subsides with little residual edema but if diffuse, chronic or recurrent, permanent damage may result with lymphedema as the end result. The management of lymphatic problems is therefore largely one of prophylaxis. An acute infection or injury to an extremity may be the beginning of permanent lymphatic damage. Let me cite a recent instance. A worker received a crushing injury to his right fourth finger with a secondary infection at the base of the digit. This responded to surgical drainage but not before the hand and forearm had become red and swollen. The complicating lymphangitis became chronic and after four years this man has destruction of many of the lymph channels draining his right hand with permanent disabling edema.

Allen and Ghormley[19] have stressed this important fact of prophylaxis so let me spend some time pointing out the important procedures indicated in any patient liable to develop a lymphedema.

Elevation should be immediately ordered and the involved extremity kept in such a position until all signs of infection have cleared or the injury healed. No matter what produces the edema the mechanism leading to a permanent swelling is always about the same. Pressure in the lymph spaces increases with a resulting dilatation of the vessels, destruction or incompetency of the valves. This in turn produces further stasis. In this static lymph fibroblasts proliferate and this in turn further slows the flow and secondary inflammation may occur with further fibrosis and scar formation. By elevation we permit rapid drainage from the extremity, keep the valves competent, prevent fibrosis and thereby prevent permanent damage.

Eradication of infection is clearly as important a step as elevation because the patient is potentially a bed case until this is done. With the discovery of the sulfonamides we have valuable chemotherapeutic agents to help eliminate the usual invader, the streptococcus. However, many workers now feel that fungus infections, epidermophytoses, may be invading agents or at least open the portal of entry for bacterial in-

vaders. Therefore, their elimination is important and their prophylaxis even more so.

Venous stasis due to varicose veins is often a cause of chronic edema through such a mechanism as I recently described. Therefore, every patient with varicose veins is a potential sufferer from lymphedema and such veins should be eradicated. The danger of this complication is even more marked if a complicating phlebitis occurs. Phlebitis without varicosities may likewise have an associated lymphangitis and a secondary lymphedema.

Filiariasis, although rare in this part of the world, is a well-known cause of elephantiasis and must not be overlooked in patients who have lived or travelled in parts of the world where this parasite is found.

Systemic disease may produce temporary edema which, if the disease is not treated, may become chronic lymphedema. Heart and renal insufficiency are the usual causes of swelling but hypoproteinemia must not be overlooked.

One must not forget that carcinoma, surgical removal of lymph glands, x-ray therapy and chronic pressure or long dependency of extremities are other causes to be eliminated wherever possible.

However, there is one group of patients with lymphatic obstruction on the basis of what appears to be a congenital defect in the lymphatic system for which there is little to be done from the prophylactic angle. Such cases have been called primary lymphedema, precox and congenital (Milroy's disease when occurring in families). Many of these do not appear until about the age of puberty.

In all cases of edema, regardless of the cause, when the patient becomes ambulatory, support of the tissues in the involved extremity must be carried out, often for a long time, until it is evident that the edema will not recur when such support is removed. Bandages, rubber, woven elastic, adhesive and non-adhesive or stockings may be used but the support must be adequate to control the swelling without blocking the arterial supply.

I have been able to demonstrate in several early cases of the congenital type of lymphedema, that after dehydration and elevation of the extremity to reduce the edema, adequate support over several years will help the growth of collateral vessels sufficiently to prevent edema.

When frank lymphedema of marked degree has developed, medical treatment can be of little avail. Removal of the fibrotic edematous lym-

phatic tissue by some form of a Kondoleon operation is the only surgical method giving results that are satisfactory. The actual technique I shall leave to the surgeon. However, medically these patients should be prepared by elevation of the involved part and dehydration to remove as much of the fluid as possible. Sulfonamides should be given for 3 to 4 days to sterilize the tissues, which often contain streptococci, and immediately postoperatively blood or plasma must be given to prevent shock.

In one hour's time I have been barely able to touch upon the principles behind the management of the diseases affecting the peripheral circulation. I hope I have stimulated your interest in this field.

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DIETARY TREATMENT OF LAENNEC'S CIRRHOSIS WITH SPECIAL REFERENCE TO EARLY STAGES OF THE DISEASE*

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THE fundamental difficulty in the treatment of Laennec's cirrhosis resides in our ignorance of the nature of the disease. In searching for factors that predispose to cirrhosis and which thus may bear upon its etiology one fact remains glaringly prominent, namely, that *alcoholism* is the most common antecedent factor in this disease in the Western hemisphere. I shall not cite the evidence for this observation, which is common knowledge. And yet, in about 30 per cent of cases seen at postmortem examination there has been no story of alcoholism. Or, if one examines data on chronic alcoholism, one finds that only a small per cent, variously estimated at from 1 to 25 per cent, develop Laennec's cirrhosis. It seems very probable that the association is intimate, but not direct; that alcoholism per se does not cause cirrhosis of the liver.

Since alcoholic beri-beri[1,2] and pellagra[3] have been shown to be similar to the endemic forms of these diseases, it seemed possible that the correlation between alcoholism and Laennec's cirrhosis also might be due to co-existing nutritional deficiency. This hypothesis seemed attractive, particularly since a high incidence of vitamin B complex deficiency was noted in our patients with this disease, and also has been reported by others.[4,5,6] With this in mind we started treating patients with Laennec's cirrhosis by means of a highly nutritious diet supplemented with vitamin B concentrates, and reported favorable results in a series of thirteen patients.[7] However, since the patients were observed for only one year, it seemed advisable to extend the program over a longer period of time in a larger number of patients. This we have done during the past five years.

Meanwhile, from different laboratories, experimental evidence has

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TABLE I

CLINICAL DATA ON PATIENTS WITH LAENNEC'S CIRRHOSIS*

	Treated Series (54)		*Control Series (386)*	
	number	*per cent*	*number*	*per cent*
Symptoms				
Weight loss	42	78	206	53
Abdominal Swelling	48	89	301	80
Peripheral Edema	46	85	236	61
Nausea and Vomiting	29	54	129	33
Hematemesis	13	24	106	27
Abdominal Pain	22	40	121	31
Signs				
Ascites	48	89	301	80
Palpable Liver	44	81	291	75
Palpable Spleen	38	70	170	44
Jaundice	34	63	252	65
Edema	46	85	236	61
Hemorrhoids	30	56	105	27
Collateral Veins	41	76	91	23
Vascular Spiders	37	68	58	15

accumulated which supports the hypothesis of a nutritional component in the pathogenesis of cirrhosis. Recent studies indicate that the feeding of yeast,[8,9] of protein,[10,11,12] and of choline[13] may afford a degree of protection against known liver poisons. Other studies suggest that the lack of certain factors contained in yeast or casein brings about fibrotic changes in the livers of rats[14,15,16,17] and rabbits.[18] The feeding of excess fat[19,20] and of excess cystine[21] also is said to produce liver cirrhosis in experimental animals. Although all these observations do not fit neatly into a single concept of the disease process, it is possible that the differences can be reconciled. The significance of these studies in relation to human Laennec's cirrhosis awaits further clarification.

So much for the evidence of a nutritional factor in the etiology.

* Condensed from previous publications (references 22, 23).

I wish now to describe some of our clinical findings; first in the treatment of patients with frank liver failure or decompensation, and second, with a group of patients who were considered to show signs of early liver damage. This work has been carried out in conjunction with Doctors Joseph Post[22] and Oscar D. Ratnoff.[23]

The first group comprises a series of fifty-four patients with decompensated Laennec's cirrhosis. By decompensated I mean that there were signs of frank liver failure, which required hospitalization. In order to establish a norm for comparison with this treated group, a series of 386 cases of cirrhosis was analyzed from the records of five New York hospitals. These will be referred to as a control group. Clinical data obtained from these two groups are recorded in Table I. Several of these symptoms and signs showed a higher incidence in the treated series than in the control series, due presumably to the fact that our patients were under close scrutiny for longer periods of time. However, it seems fair to conclude that the symptoms and signs were comparable in the two groups, and that the severity of the underlying disease process also was comparable.

In contrast to the usual American diet prescribed for liver disease, which is high in carbohydrate but low in protein and fat, the present diet is rich in protein and ample in carbohydrate and fat. It contains 3,591 calories and it has the following proportions: Protein 139*, Fat 175, Carbohydrate 365. The diet consists chiefly of meat, milk, eggs, fruit, and green vegetables. Meat is served twice daily; milk five times daily—three times with meals and two times with 25 grams of powdered brewer's yeast. It is advisable to feed the yeast in graded, increasing doses up to the final amount. Occasionally patients cannot tolerate brewer's yeast. For these, oral vitamin B complex has been substituted in the form of liquid yeast concentrates. In addition, thiamin chloride (5 mgm.) is injected i.m. daily and liver extract (5 cc.), twice weekly. The art of nursing is put to the test, for it involves feeding a patient to whom food often is loathsome. Regard for his likes and dislikes, encouragement, and infinite patience are needed. The nursing and dietetic care, particularly during the critical period of decompensation, should be as meticulous and vigilant as that given the patient with typhoid fever. The intake of each meal should be charted in order to keep ac-

* Includes protein in brewer's yeast.

count of the actual consumption. It is the amount consumed rather than the amount served that counts.

In patients with ascites the salt intake is restricted only by the exclusion of a salt shaker from the tray, and fluids are allowed up to 2000 cc. daily. Too rigid restriction of salt and water is harmful to these patients, and has been observed to precipitate symptoms of hypochloremia. It should be realized that with each abdominal tap considerable salt is removed. Nonetheless, it is desirable to tap abdominal fluid before the patient is distended too much, for this interferes seriously with the appetite. Mercurial diuretics may be injected once or twice weekly together with ammonium chloride by mouth, in order to space out the intervals between paracenteses.

For the sake of simplicity in discussing results of this treatment, the patients were placed in three groups according to their clinical course:

Group A: *Those patients who showed signs of progressive failure.* There were twenty-two in this group. Of these eleven died within one month, and only four survived more than 5 months after entry to the hospital. It is evident from this short period of survival that they were severely ill at the time of admission.

Group B. *Those patients who made partial improvement.* There were twelve in this group. Five showed satisfactory improvement, as gauged by the loss of ascites and by changes in their laboratory tests, but they were classified in this group because of a limited follow-up after discharge from the hospital. Three others have remained free of ascites, after having required abdominal taps in the past, but they are not in robust health. Four others made similar improvement, but they subsequently died, after being ascites-free for over 2 years in each instance.

Group C. *Those patients who showed signs of "clinical recovery."* Their improvement fulfilled three criteria: (1) Gain in weight and strength permitting the patient to resume his previous activity; (2) loss of ascites, edema, and jaundice without recurrence; (3) changes of serum proteins, Takata-Ara, and bromsulfalein dye tests towards normal values.

By this I do not wish to imply that the laboratory tests of this latter group were completely normal, nor that the histological changes were reversed. However, it was clear that the process had been arrested, or reversed to a degree that allowed the patient to live a normal life for

several years. There is no doubt that there will be relapses, and that as a group their life span may be shorter than that of persons who have not had the disease.

In order to determine whether treatment altered the course of the disease significantly, comparison was made with the control series of 386 patients previously mentioned. It was shown that approximately 7 per cent of the control series, in contrast to 60 per cent of the treated series, experienced the spontaneous disappearance of ascites. The period of survival of patients after the onset of ascites showed the following differences: At six months 57 per cent of the controls were alive in contrast to 72 per cent of the treated series; at one year there were 37 per cent of the controls and 57 per cent of the treated series; at two years there were 22 per cent of the controls and 45 per cent of the treated series.

The data on these fifty-four patients were obtained from 1936 to 1941, and they are reported in detail in a previous publication.[22] Although the series has been increased by many patients in the past two years, our subsequent experience has been much the same. From the Mayo Clinic, Fleming and Snell[24] recently reported encouraging results in fifty cases of decompensated Laennec's cirrhosis, treated with a high protein diet together with vitamin concentrates. Twenty patients (44 per cent) showed significant clinical improvement. Of this group, ascites had disappeared in eleven, and had diminished in five. Keefer and Fries[25] recently described seventy cases of "fatty liver." Of these, nineteen were latent cases, whereas fifty-one showed signs of hepatic insufficiency, such as jaundice and ascites. The authors believe that a high carbohydrate, low fat, medium protein diet together with vitamin concentrates is of therapeutic value.

Since our series of fifty-four patients had arrived when liver damage was extreme, there was little hope of obtaining a high per cent of clinical recoveries. However specific this or any other treatment may be, the success will be limited until the disease is diagnosed earlier. Therefore, we have tried to recognize earlier stages of the disease, even though the means of diagnosis are still inadequate.

The high incidence of nutritional deficiency, especially of the vitamin B complex, in Laennec's cirrhosis suggested that a nutritional factor might play a role, and treatment was based upon this hypothesis. It therefore seemed possible that patients who entered the hospital be-

TABLE II

SIGNS OF MALNUTRITION IN 33 PATIENTS WITH VITAMIN DEFICIENCY DISEASES AND IN 54 PATIENTS WITH LAENNEC'S CIRRHOSIS

	Vitamin Deficiencies (33)		*Laennec's Cirrhosis (54)*	
	number	*per cent*	*number*	*per cent*
Weight Loss	21	64	42	78
G. I. Distress	18	55	29	54
Polyneuritis	26	79	21	40
Smooth Tongue	23	70	32	60
Dry Skin	19	60	34	63
Macrocytosis	12	36	21	40

cause of malnutrition alone would show signs of occult liver damage. We selected those who entered because of polyneuritis, sprue, pellagra or scurvy, but without overt signs of liver damage such as jaundice, ascites, or edema. However, since these patients were sent to us from clinics that knew of our interest in liver disease, the selection of these patients undoubtedly was biased. It is also unfortunate that the majority were alcoholics, but in this climate it is difficult to divorce nutritional deficiency from alcoholism. Despite these objections the data are of interest.

In Table II the incidence of signs of malnutrition in thirty-three patients with vitamin deficiency diseases is compared to that of fifty-four patients with Laennec's cirrhosis. There is a close similarity between the two groups.

In Table III are listed the signs of liver damage in the same groups of patients. There is similarity here as well, but also several distinct differences. Splenomegaly and vascular "spiders" were seen commonly only in the mature form of Laennec's cirrhosis. Hypoalbuminemia occurred in 33 per cent of the group with vitamin deficiencies in contrast to 96 per cent of those with cirrhosis. However, elevated serum globulin, increased bromsulfalein dye retention and positive Hanger flocculation reactions appeared commonly in both groups of patients. Hence, the latter three tests may be considered to be sensitive indices of liver damage.

TABLE III

SIGNS OF LIVER DAMAGE IN 33 PATIENTS WITH VITAMIN DEFICIENCY DISEASES AND IN 54 PATIENTS WITH LAENNEC'S CIRRHOSIS

	Vitamin Deficiencies (33)		*Laennec's Cirrhosis (54)*	
	number	*per cent*	*number*	*per cent*
Palpable Liver	16	48	44	81
Palpable Spleen	2	6	38	70
Epistaxis	7	21	25	46
Vascular "Spiders"	3	9	37	68
S. Albumin<4 gms. %	11	33	52	96
S. Globulin>3 gms. %	21	64	45	83
*Bromsulfalein>10%	28	85	52	96
Positive Flocc. Reaction	14	64	49	91**
No signs	4	12		

* Retention of bromsulfalein dye at ½ hr. Method employs 5 mgm /kilo.
** Takata-Ara reaction.

TABLE IV

DATA ON PATIENT D.T. INDICATING TRANSITION FROM EARLY TO DECOMPENSATED STAGE OF LAENNEC'S CIRRHOSIS

	1st Entry		*2nd Entry*			
	Adm.	*Disch.*	*O.P.D.*	*Adm.*		
	6/40	9/40	5/41	9/42	11/42	1/43*
Palpable Liver	++	+	+	+++	++	++
Palpable Spleen	0	0	0	+	+	+
Vascular "Spider"	++	+	++	++	+	+
Jaundice	0	0	0	+	0	0
Ascites	0	0	0	+++	0	0
S. Albumin gms. %	4.4	4.3	4.1	2.9	3.7	4.1
S. globulin gms. %	2.9	2.6	4.0	2.8	3.3	2.9
Bromsulfalein %	44	34	64	70	60	53
Flocculation R.	±	0	+++	+++	+++	+++

* Data obtained since presentation on 12/15/42.

The question may be raised as to whether such cases actually represent an early stage of Laennec's cirrhosis. I believe that they do. As an example, I wish to describe the findings in a patient who was observed for 2½ years and whose course showed a transition from the early "subclinical" to the decompensated stage of Laennec's cirrhosis (cf Table IV).

Case History: A 43 year old entertainer gave a story of alcoholism and a meagre diet. Her complaints at entry (June 1940) were weakness, fatigue, anorexia, epigastric fulness and distress. The following signs were noted: a large, firm liver, several vascular spiders, increased dye retention, minimal flocculation reaction, normal serum proteins. While in the hospital she was treated with the nutritious diet and vitamin supplements previously described, and after 2 months she was discharged as improved. The liver edge had receded, and vascular spiders had decreased in number. The dye test, however, was still abnormal. She resumed her previous dietary habits, and was seen at irregular intervals in the clinic. One year later (May 1941) the earlier symptoms had reappeared. Tests at this time showed elevated serum globulin, strongly positive flocculation reaction, and increased dye retention. Hospitalization was refused by the patient.

In January, 1942 the patient donated a pint of blood to the Red Cross. Shortly after this her teeth were extracted, and her diet became reduced to alcoholic beverages. In August signs of liver failure developed, including jaundice, massive ascites, palpable liver and spleen, and reduced serum albumin. She entered the hospital in September. After two months of dietary treatment these signs have partially regressed. Jaundice and ascites have disappeared. Serum albumin has increased. The patient is ambulatory and she feels well.

This patient, then, exhibited a satisfactory response to treatment when liver damage was slight, relapse on discontinuing therapy, and a second response to treatment after failure set in. It is likely that her liver failure would have been prevented had this patient been conscientious two years ago when changes were minimal.

In general, the changes in this group of patients with symptoms and signs of early liver damage respond readily to the dietary treatment previously described. It is in the treatment of this early stage of liver disease that preventive medicine should be most useful in the future.

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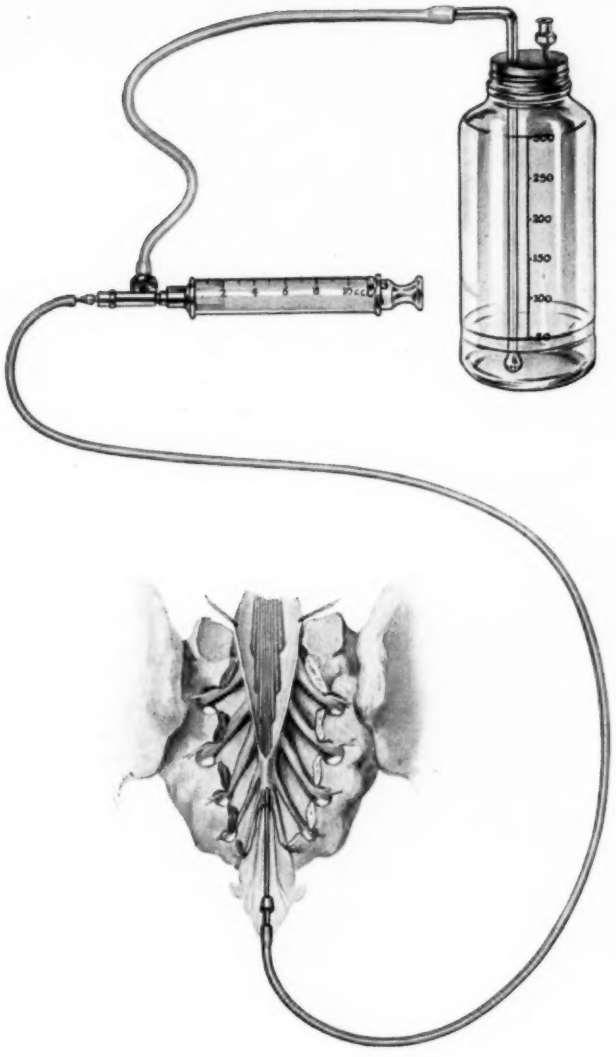


FIGURE 2—*Apparatus with needle properly placed in sacral canal.*

The Innervation of the Uterus and Birth Canal in Pregnancy

The Bulletin acknowledges with appreciation the courtesy rendered by The Physician's Bulletin and Eli Lilly and Company which has provided the accompanying Figures 1 and 2.

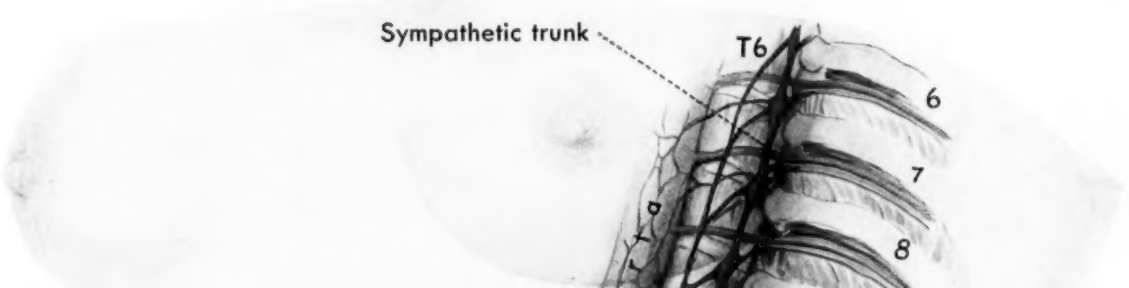
FIGURE 1

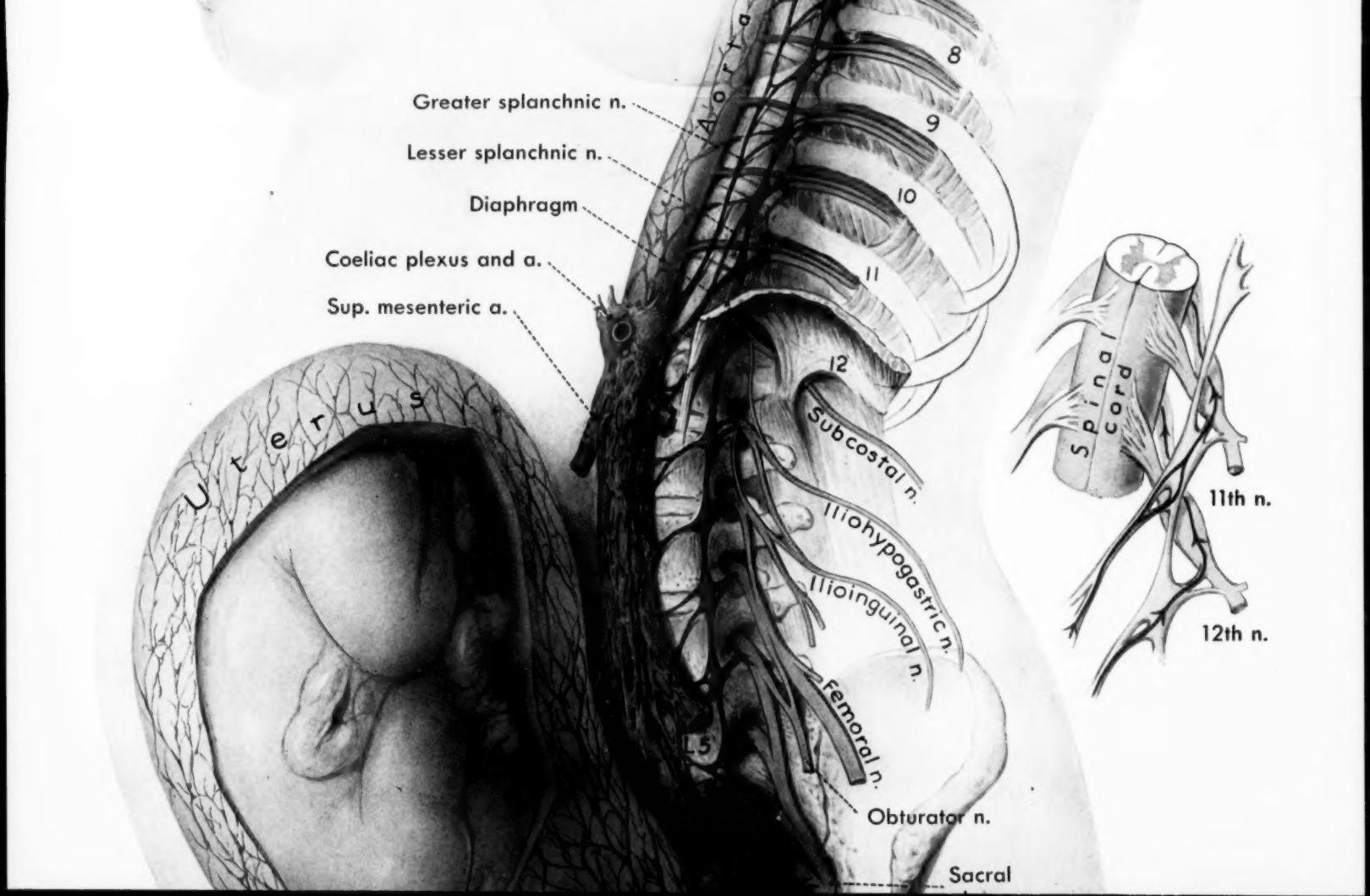
The Innervation of the Uterus and Birth Canal in Pregnancy

THE sensory nerve fibers of the uterus are shown in red. They constitute visceral afferent fibers and are functionally independent of the autonomic nervous system although coursing through the pelvic, hypogastric, and aortic plexuses before connecting with the dorsal root ganglia of the eleventh and twelfth thoracic nerves in which their nerve cells are located. The insert shows details of the connections. The sensory supply to the cervix and upper vagina travels in the sacral parasympathetic nerves shown in green. It is also functionally independent of the autonomic system. The sensory and motor supply of the lower vagina, perineum, and pelvic floor travels in the perineal and pudendal somatic nerves. All of the spinal (somatic) nerves are shown in yellow.

The motor supply of the uterus is autonomic and involves both sympathetic and parasympathetic efferent components. The sympathetic division is shown in purple with the exception of the part concerned with uterine motility which is shown in blue. Clinical evidence indicates that the motor fibers to the uterus leave the spinal cord at higher levels than the tenth thoracic nerve whence they pass through the aortic, hypogastric, and pelvic plexuses. Visceral efferent fibers believed to be motor to the circular muscle of the lower uterine segment and cervix and possibly inhibitory to the remainder of the uterus travel through the parasympathetic pelvic nerves shown in green.

Clinical study verifies that (1) blocking the sacral nerve roots abolishes the pain of distention of the birth canal, paralyzes the skeletal muscle of the perineum, and abolishes tone in the smooth muscle of the cervix; and (2) extending the block to include the eleventh thoracic root abolishes the pain of uterine contractions without impairing their force. It suggests that extending the block to the sixth thoracic nerve or higher may impair the strength of uterine contractions.




Greater splanchnic n.
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Diaphragm
Coeliac plexus and a.
Sup. mesenteric a.
Aorta
8
9
10
11
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Subcostal n.
Iliohypogastric n.
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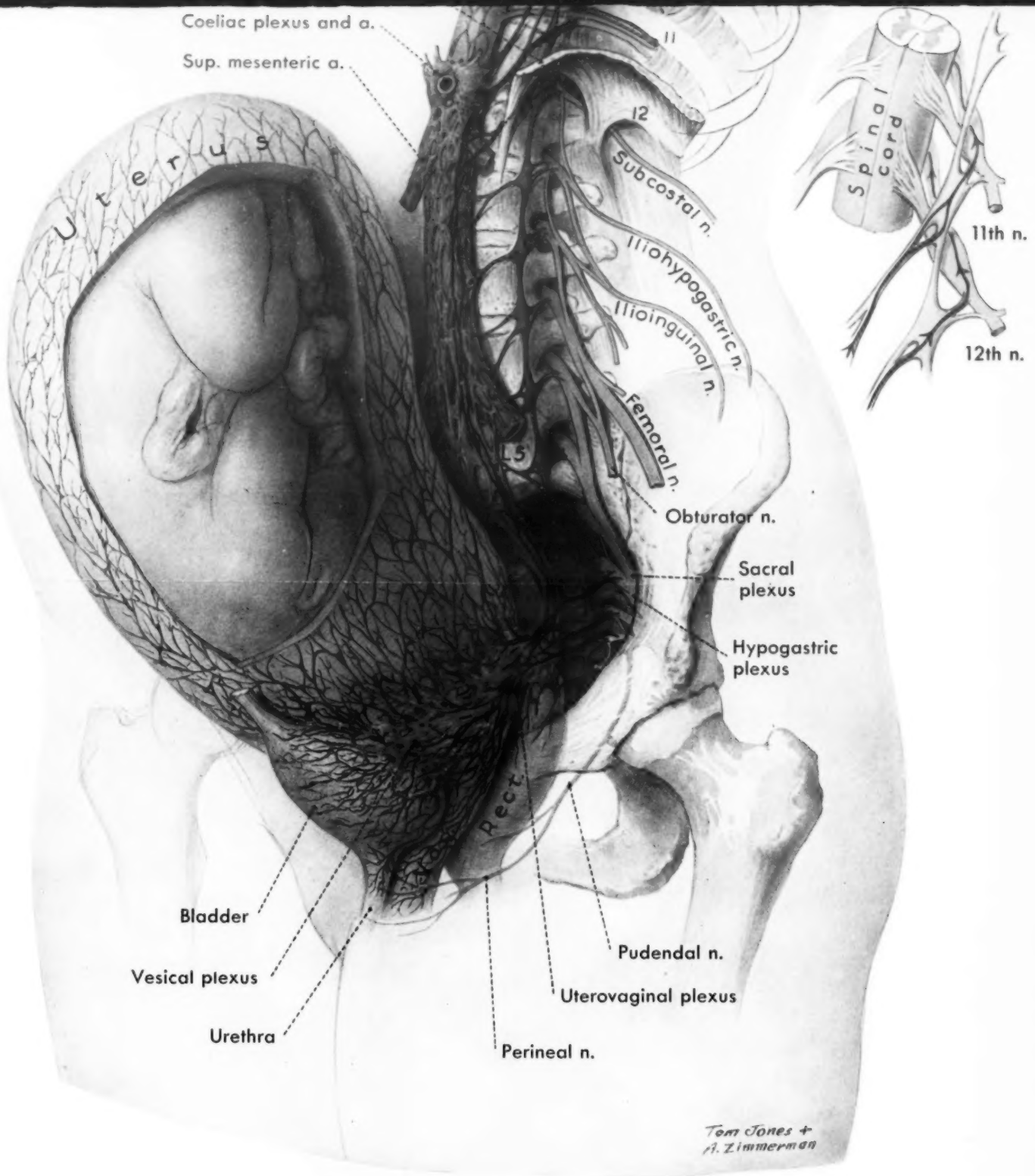
Femoral n.
L5
Obturator n.
Sacral
Uterus
Spinal cord
11th n.
12th n.


Coeliac plexus and a.
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L5
Obturator n.
Sacral plexus
Hypogastric plexus
Rect.
Bladder
Vesical plexus
Urethra
Perineal n.
Pudendal n.
Uterovaginal plexus
Spinal cord
11th n.
12th n.
Tom Jones +
A. Zimmerman

THE PRESENT STATUS OF CONTINUOUS CAUDAL ANALGESIA IN OBSTETRICS*

WALDO B. EDWARDS AND ROBERT A. HINGSON

Passed Assistant Surgeons, U.S.P.H.S.

OUR thesis had been postulated for us by T. J. Stander in the last edition of Williams' Obstetrics:[1] "If satisfactory analgesia were always possible, drugs having an amnesic action could be entirely dispensed with."

Our experience with Continuous Caudal Analgesia has presented convincing evidence that labor and delivery does occur with almost perfect comfort for the parturient, without the necessity of any amnesic or an anesthetic drug.

Our approach to the problem of safe painless childbirth has followed the application of the principles of regional nerve block to those nervous pathways concerned with the transmission of painful stimuli excited during labor and delivery. While our efforts for several years were directed toward the solution of the problem, we were encouraged by the discussion of this subject by DeLee:[2] "Why put the whole body under anesthesia when you are going to operate on one part? There are three reasons for local and regional anesthesia: first, its availability; second, its safety from complications; and third, the after results."

In adding the continuous feature to the time-honored and established procedure of caudal analgesia, we give full credit to the pioneers, who for four decades have used the method in the several branches of surgery and obstetrics. The single caudal injection was introduced independently and simultaneously by the French surgeons Sicard[3] and Cathelin[4] in the year 1901. Within a short time Cathelin was able to report a thousand cases in which the procedure was used on man, mainly for the relief of bed-wetting. Cathelin envisioned but did not attempt use of the method to alleviate the pains of labor.

The single injection technique of caudal analgesia has been more widely used in surgery than in obstetrics. Läwen[5] first described such an application in 1910. Others took up the method, finding it well-suited

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for operations by the perineal approach in the fields of urology, proctology and gynecology. By 1920 Zweifel[6] was able to find 4,200 cases recorded in the literature. In this large series there were ten postoperative deaths. Seven of them seemed obviously independent of the anesthesia; the remaining three occurred respectively a few seconds, seven minutes, and ten minutes after the sacral injection of 0.6 gm. or more of procaine. Six-tenths gram of procaine is now considered a rather large dose for such an injection.

Clinical reports concerning single-injection caudal analgesia in surgery are extremely numerous. Among the earliest American publications are those of Harris[7] in 1915, and Lewis and Bartels[8] in 1916 and Thompson[9] in 1917. Oswald S. Lowsley of New York City reported seventy cases in 1923. John S. Lundy of the Mayo Clinic has reported 15,000 cases without a death. Incidentally, this is the largest series under any single form of anesthesia of that clinic without a fatality. Referring to both caudal and trans-sacral analgesia, he says: "Sacral block is one of the most satisfactory methods available to the anesthetist in the whole field of anesthesia. It is difficult only for those who will not take the trouble to train themselves in the technique."

The first actual application of caudal analgesia to obstetrics was apparently made by Stoeckel of Marburg in 1909. Using procaine, which had not been available to Sicard and Cathelin, he attained a considerable measure of success in relieving the pangs of childbirth in 141 normal cases. With the procedure he was able to distinguish two types of pain during labor, those which we now associate respectively with uterine contractions and with distention of the birth canal. Stoeckel was impressed especially by the great relaxation of the pelvic floor and perineum, the lack of impairment of uterine contractions, and the vigor and well-being of the babies. While acknowledging freely the need for technical improvement in the method, he emphasized its safety and the load of anxiety it lifts from the physician's shoulders in the conduct of labor.

Schlimpert of Leipzig also became interested in the method, and in an address in the United States in 1913[10] reported on its use in approximately fifty cases.

On this side of the Atlantic Meeker and Bonar,[11, 12] Oldham[13, 14, 15] and Rucker[16, 17] seem to have been pioneers in its obstetrical use. Meeker reports specifically on ninety cases, Oldham on more than 500, and

Rucker over one thousand. Since 1930 articles have been published by Cleland,[18] Baptisti,[19] Poole,[20] Hopp,[21] and Lahmann and Mietus.[22] The largest series in this group is that of Lahmann and Mietus with 400 cases.

For all of these men the only serious disadvantage of the single injection method was its limited duration. It did not suffice for the entire period of labor, and its usefulness in delivery was made uncertain by the unpredictable time of that event. All too often the effect wore off before delivery in primiparae and was induced too late to become fully effective for delivery in multiparae.

The introduction of the continuous feature has eliminated this difficulty. It is now possible to maintain the parturient free of pain from the time labor is definitely established until relief is no longer needed.

In the development of continuous caudal analgesia, it became necessary to find a drug that would prove safe for mother and child while relieving the pains of labor through regional nerve block.

In our search for this drug we used all of the recognized cocaine derivatives and cocaine substitutes in varying concentrations and in different vehicles. In our opinion metycaine most nearly met these criteria. It has the most lasting effect and produces no toxic symptoms.

Our experience confirmed the earlier observations of Ferguson,[23] Lundy,[24] Tuohy,[25] Fulton,[26] Mentzer,[27] and Lahmann and Mietus.[22] To more than one thousand surgical and obstetrical patients we have administered more than four thousand grams of metycaine without a single toxic reaction in mother or baby that could be attributed to the anesthetic solution. Nor has there been a single case of post-analgesia neuropathy. The patients were under this form of analgesia from one to thirty-three hours for an average of four hours and thirty minutes. This represents approximately 7.5 mg. of the drug per kilogram of body weight per hour.

It is necessary to multiply this dose by six times before comparable hourly doses in pregnant rabbits will produce signs of toxemia as evidenced by convulsions. It is necessary to multiply this dose by ten times before an appreciable number of fetal rabbits will be born dead.[28] These studies were carried out on more than fifty pregnant rabbits one and two days before delivery. In most of them hourly doses of the metycaine were given for ten consecutive doses.

Also of fundamental importance in the production of continuous caudal analgesia is the special apparatus consisting of: (a) Graduated

reservoir bottle, (b) Rubber tube and metal sinker, (c) Special automatic two way 470V valve with Luerlok connection, (d) One mm. garter tubing four feet in length, (e) Special malleable, stainless steel needle, (f) Small hose connector for aspiration (Figure 2).

The most important part of the apparatus is the malleable needle. This needle is so constructed that it will assume the curvature of the sacral canal for many hours under considerable stress without breakage and without obliteration of the lumen. The development of this needle has materially lessened the dangers incurred with the ordinary types of steel needles. In our series it has been used more than four hundred times without breakage. However, until experience has been sufficient to test the durability of the needle, we recommend that it be discarded after five complete labors and deliveries.

Anatomic and Physiologic Considerations

A fundamental knowledge of the anatomy of the sacral area and of the nerve supply to the uterus is a prerequisite for success in continuous caudal analgesia. The anatomical proximity of the sacral hiatus to the nerves of the pelvis, perineum and lower extremities makes this method applicable for operative work in these regions.

Centuries ago the Greek anatomists named the large triangular bone at the lower extremity of the vertebral column the "sacred bone" or the sacrum. Since it was the last bone of the body to disintegrate in the grave and since it contained the bony canal into which the animal spirits or the soul of man were supposed to migrate during sleep, it came to have a special emphasis and significance. When we consider that the nerve pathways of locomotion, micturition, defecation, parturition, and reproduction traverse the sacral canal, it is easy for us to understand why the Greeks thought the soul of man was located here.

The peridural space surrounding the dura mater from the foramen magnum to the hiatus sacralis comprises the area between the dura mater and the periosteum lining the spinal canal. The sacral canal is a continuation of the spinal canal, but usually at the second sacral segment communication between these two parts is interrupted by the closure of the dura around the nerve trunks. In dissection of cadavers we found that the dura sometimes encircles the spinal nerves of the cauda equina and the filum terminale all the way to the fourth or fifth sacral segment. In these instances spinal fluid can be obtained by inserting a short needle

into the sacral hiatus. This phenomenon has been observed by us only three times in 1,000 caudal injections. The occurrence of anomalies and malformations of the vertebral and spinal canals should be kept in mind continuously.

Upon the outer surface of the dura, in the epidural space, especially at the sides are extensive venous plexuses and loose adipose tissue.

The sacral canal terminates below in the hiatus sacralis, forming a triangular opening, the sides of which are marked by the bony ridges known as the sacral cornua. This opening varies in size and shape in different individuals. It may be abnormally large, owing to a deficiency in one or more of the vertebral arches, or it may be reduced to the extent of bony obliteration (Figure 3). These sacral specimens were obtained in the department of anatomy of the Jefferson University Medical School in Philadelphia.

In working in the necropsy material in the same laboratory in conjunction with Doctors Vaux and Lull we found that when 30 cc. of solution was injected into the peridural space, the uppermost extent of the dye was the sixth dorsal segment. In all of them the dye extended on both sides as high as the tenth dorsal segment. This is exactly the picture we have been able to produce on the living parturient. Therefore our initial dose is 30 cc. of one and one-half per cent metycaine, and in the majority of the patients there will be an analgesia produced as high as the line midway between the pubis and the umbilicus. We have found that whenever such a level of analgesia is attained, the pains of labor are relieved.

Nerve Supply to the Uterus

In 1893 Head, the English physiologist, postulated that the sensory nerve supply to the uterus was located in the fibers of the sympathetic nervous system in the region of the lower dorsal segments. Cleland[18] in 1933 more accurately located these pathways as coursing through the sympathetic ganglia of the eleventh and twelfth dorsal segments.

Our work has substantiated these contentions. At the present time we believe that the nerve supply to the uterus is divided into three separate anatomical components. These we have attempted to show in the lantern slide of the anatomical drawing done for us by Tom Jones (Figure 1).

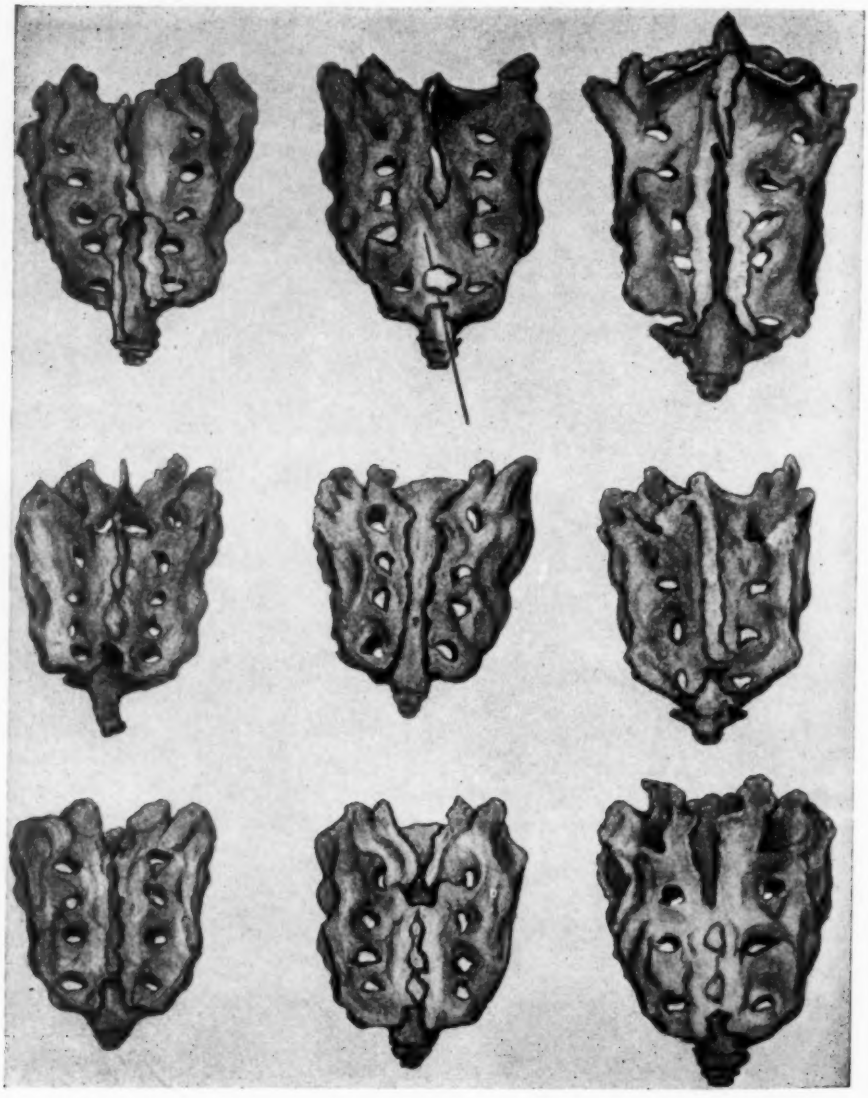

Figure 3: Sacral specimens, showing variations in the anatomy of the human sacrum.

Absolute Anesthetic Contraindications

1. Local infection at the site of the area to be injected, such as a furuncle or a pilonidal cyst.

2. A low lying dura mater, as determined by an aspiration of spinal fluid. This is an absolute contraindication. In such a case the needle is to be withdrawn and the case handled in some other way.

3. Deformity of the sacrum with bony obliteration of the sacral hiatus. This condition is extremely rare. It occurs perhaps less than one time in 500 cases.

4. A history of sensitivity to the drug.

Relative Contraindications

1. The unusually obese individual in whom the sacral hiatus cannot be palpated. Already in three clinics we have seen beginners with the technique insert the needle and after several minutes declare the method was no good for these particular cases. Rectal examinations revealed the presence of the needle anterior to the sacrum and in two cases through the wall of the rectum. We would like to emphasize that blind prodding with a needle is not good anesthesia nor safe obstetrics.

2. The hysterical patient would also be a poor candidate for this regime.

3. Repeated aspirations of blood through the caudal needle indicating that the needle is in a vein or a capillary plexus. The skilled anesthetist knows how to manipulate the needle outside of such a site and then continue with the injection. The beginner will learn only through special training.

Complications

We hope that by emphasizing our complications, the medical men who use this method after us will avoid some of our mistakes and our difficulties.

1. Broken needles. Our most frequent complication in the early part of our series when we were using different types of needles, was breakage of the needle at the hub. After twelve such experiences in four of which we had to make surgical incisions, we have eliminated this flaw by perfection of a malleable stainless steel needle.

2. Infection. In our series of more than one thousand obstetric and

surgical continuous caudal analgesias, there has been only one infection. This was an obstetrical case which developed a peridural abscess with Staphylococcus aureus and a bacteriemia uncontrolled by rigid sulfonamide therapy. This patient died on the thirty-first day after delivery.

In analyzing the portal of entry of the infection three sources must be kept in mind:

1. The skin of the patient through which the needle was inserted.
2. The injected solution.
3. Some break in technique on the part of the operator in making subsequent injections. We are working at the present time on perfecting a syringe whereby contamination by the operator will be impossible.

We have had a few minor systemic complaints which we have been able to remedy with slight modifications of technique and management. These have been slight, temporary headache at the time of initial injection in an occasional case; back-ache between the shoulders when the parturient spends too much time on her back; a feeling of an ache or pressure along the course of the sciatic nerve as the solution is injected.

Besides the complications listed, our patients have had comfortable labors and deliveries.

The technique of administration is one that must be learned by actual experience. We consider that more than 80 per cent of the injections are easier than lumbar puncture. An initial injection of 30 cc. of metycaine solution and subsequent injections of 20 cc. every forty minutes to one hour will keep the average obstetrical case comfortable.

The key-hole whereby the entire problem of pain in childbirth may be unlocked is the sacral hiatus. The malleable caudal needle is the key. The adequate dosage of metycaine necessary to block the pathways of pain involved in parturition is the combination of that lock.

After managing the obstetrical labors and deliveries of 660 cases with only one maternal fatality and the deliveries of 654 live babies, we are convinced that in the hands of doctors specially trained, painless childbirth can be managed by continuous caudal analgesia in the overwhelming majority of all hospital patients. One-fourth of these deliveries were carried out in our own hospital; one-fourth of them were carried out in the Philadelphia-Lying-In and Jefferson University Hospitals under the direction of Dr. Norris Vaux and Dr. Clifford Lull. The other half were accomplished in recognized obstetrical teaching

hospitals associated with twenty-three medical schools under the direction of the members of the American Society of Obstetricians, Gynecologists and Abdominal Surgeons, where we appeared in the United States and Canada on invitation for purposes of demonstration and lecture.

The interpretation of the obstetrical findings and the management of the cases from this standpoint will now be discussed by Doctor Edwards.

DeLee said:[2] "It is the duty of the obstetrician to mitigate the sufferings of natural labor."

The amnesics to screen painful memories, the hypnotics to promote sleep, the anesthetics to block out all central perception have all been used with varying degrees of satisfaction to patient and obstetrician. Caudal block with a single injection is useful but produces analgesia for only a limited period. We believe that continuous caudal analgesia will be an addition to the obstetrician's armamentarium. In our hands it has had no bad effect on either mother or child and has been successful in making labor and delivery painless.

We believe it to have the following advantages:

1. There is freedom from pain beginning five to fifteen minutes after the first injection and this painless state can be maintained as long as necessary, by repeated injections.

2. Consciousness and motor function on the part of the mother are not impaired.

3. There is no interference with the rate and strength of uterine contractions.

4. The respiratory and other vital mechanisms of the child are not obtunded.

5. The duration of labor has been shortened in the majority of our cases.

6. The management of unfavorable fetal positions is facilitated.

7. Postpartum hemorrhage is minimized.

8. The incidence and severity of maternal postpartum complications are reduced.

9. There has been no observed adverse effect in the course of cardiac or pulmonary disease in our few observed cases.

10. Patients having metabolic diseases necessitating special feeding can continue their diet while under caudal anesthesia.

The course of labor under continuous caudal analgesia presents some points of difference.

Cervical dilatation is usually rapid in both primipara and multipara, and the first stage of labor is materially shortened, an effect apparently due largely to cervical and perineal relaxation. Likewise, the early part of the second stage is expedited. The later part of the second stage is definitely prolonged, since uterine contractions alone are seldom adequate for the final delivery. Thus, precipitation is rarely seen. Because she is unaware of her uterine contractions the patient lacks any compulsion to strain. The parturient is, however, able to add the expulsive power of her abdominal musculature and diaphragm to that of uterine contractions and spontaneous delivery is not difficult.

The cervix and perineal tissues are so completely relaxed that outlet forceps and episiotomy, if necessary, are relatively simple procedures. The lack of expulsive desire is in many ways an advantage to the accoucheur, since the patient is able to coöperate fully in giving him complete control of the progress of the head over the perineum.

Especial care is necessary to clear the respiratory passage of the infant at the first possible opportunity, for the babies are usually ready to breathe the instant their noses cross the perineum. This quick onset of spontaneous respiration is one of the striking and consistent observations in babies delivered under caudal. Thus we have no resuscitation problem.

The rapid and normal separation and expulsion of the placenta from the uterus without the administration of oxytocics has been almost without exception in our experience. The average measured blood loss has been from 40 to 90 cc. Often the loss from the episiotomy exceeds in volume that from the uterus. Postpartum complications are conspicuously absent. In only one case was there a retention of the placenta and this was a cornual implantation that was extracted manually. The average duration of labor from the inception of analgesia has been six hours. Of the patients 80 per cent were primiparae and analgesia was usually begun as soon as the onset of labor could be definitely ascertained.

During the course of labor and immediately after delivery, the patients may be given a regular diet, since the method does not interfere with gastrointestinal function.

Continuous caudal analgesia should be used to relieve pain. If the parturient is not in actual need of relief there is obviously no indication for its use. It should be started only when labor has definitely begun.

Ideally the expectant mother should be having hard pains at two to three minute intervals with effacement of the lower uterine segment and one to two cms. cervical dilatation.

This method will not be entirely satisfactory in the neurotic subject.

Placenta praevia and marked disproportion between the child and the birth canal, are definite contraindications. In placenta praevia there may be severe hemorrhage because of cervical relaxation. This analgesic agent will not relax a contracted pelvis.

The mechanics of delivery can be carried out according to the preference of the obstetrician. We do not advocate that any individual change his method. At no time should he become the slave of the method, but he should keep the method his slave. However, it will soon be noted that extreme relaxation of the cervix and perineum are features of continuous caudal analgesia which greatly facilitate the handling of abnormal presentations, including occiput posterior, transverse arrest and breech presentations.

Dr. Hingson and I want to point out that we have modified caudal analgesia so that it may be employed for as long a period as desired. We have, with help from an instrument manufacturer, secured a better needle and a satisfactory apparatus. With these changes we have applied the method in obstetrics. It is, we hope and believe, a worthwhile addition to pain relieving procedures during childbirth. We present it to you, not as the final word on the subject, but for your evaluation, trial and report. We would reëmphasize that the method is best performed by a specialist, in a hospital.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

FEBRUARY 4—*The New York Academy of Medicine.* Executive session—Reading of the minutes. ¶ Papers of the evening, scientific program in cooperation with the Section of Medicine and the Section of Surgery—a] Is essential hypertension of renal origin? Irvine H. Page, Director of Clinic Research, Lilly Clinic, Indianapolis City Hospital: Homer W. Smith, Professor of Physiology, New York University, College of Medicine: b] Value of surgery in the treatment of hypertension, R. H. Smithwick, Instructor in Surgery, Harvard Medical School. ¶ Report on election of Fellows.

FEBRUARY 18—*The Harvey Society in affiliation with The New York Academy of Medicine.* The Fifth Harvey Lecture, "Some Internal Factors Limiting Growths," William J. Robbins, director, New York Botanical Gardens.

SECTION MEETINGS

FEBRUARY 2—*Dermatology and Syphilology* ¶Presentation of cases—a] Cases from the Mount Sinai Hospital; b] Miscellaneous cases. ¶ Discussion. ¶ Executive session.

FEBRUARY 4—*Surgery*—The Section of Surgery combined its scientific program with the Stated Meeting.

FEBRUARY 9—*Combined meeting of Neurology and Psychiatry and the New York Neurological Society.* ¶ Papers of the evening—a] The neural mechanism of paralysis agitans, Roland M. Klemme (by invitation); b] Modification of spastic hemiplegia by cortical excision, Jefferson Browder; Discussion, Tracy J. Putnam, Samuel Brock, Charles Davison; c] Endopsychic factors in the causation of traumatic neuroses, Sandor Lorand; d] Psychiatric reactions to the war as seen in civilians and soldiers referred to a mental hospital, Curtis T. Prout—Discussion, A. A. Brill, Ernst Kris (by invitation). ¶ Executive session of the Section.

FEBRUARY 15—*Pediatrics*—The Section held a combined meeting with the New York Roentgen Society.

FEBRUARY 15—*Ophthalmology.* ¶ Executive session, reading of the minutes. ¶ Papers of the evening—a] Some observations on visual functions in strephosymbolics, Samuel T. Orton. General discussion. b] Chronic orbital myositis, John H. Dunnington, R. N. Berke (by invitation). Discussion—John McGavic (by invitation); c] The relationship between intraocular and intracranial hemorrhage in rupture of aneurysm of the circle of Willis, James N. Greear, Jr. (by invitation). Discussion — Algernon B. Reese; d] Recession of the inferior oblique, James W. White. Discussion—John H. Dunnington, L. W. Hughes (by invitation); e] Epidemic keratoconjunctivitis, Murray Sanders. Discussion —Allson Braley (by invitation).

Medicine—The Section did not hold its regular meeting on February 16, as it combined its scientific program with that of the Stated Meeting on February 4.

Genito-Urinary Surgery—The Section held no meeting in February.

FEBRUARY 17—*Otolaryngology*—Reading of the minutes. ¶ Papers of the evening—a] 1. A few details and technical hints in rhinoplasty. 2. Operation for traumatic deformity of the nose and forehead (colored motion picture), Gustave Aufricht; b] Reconstruction of the external ear, Jerome Pierce Webster; c] New techniques in rhinoplastic surgery (Moving picture and slide demonstration), John A. Cinelli (by invitation), Gerhard H. Cox (by invitation), Vilray P. Blair, St. Louis, Missouri. ¶ General discussion. ¶ Executive session.

FEBRUARY 19—*Orthopedic Surgery.* ¶ Reading of the minutes. ¶ Papers of the evening—a] The occurrence of scoliosis in anterior poliomyelitis, Frederick vom Saal (by invitation); b] A critical analysis of the management of paralytic scoliosis, Samuel Kleinberg; c] The end-results of correction and maintenance by surgical fixation, John Cobb. Discussion—Alan DeForest Smith. ¶ General discussion. ¶ Executive session.

FEBRUARY 23—*Obstetrics and Gynecology.* ¶ Executive session, reading of the minutes. ¶ Case reports, Streptococcus viridans pneumonia (prepartum and intrapartum) and pulmonary embolism (postpartum) with recovery, Haig Carapaytan (by invitation). ¶ Papers of the evening—a] The value of pelvioradiography in the management of dystocia, Arthur Weinberg (by invitation), Samuel J. Scadron; b] Continuous caudal analgesia in obstetrics, Robert A. Hingson (by invitation), Waldo B. Edwards (by invitation). ¶ General discussion.

AFFILIATED SOCIETIES

FEBRUARY 15—*Combined Meeting of New York Roentgen Society and the Section of Pediatrics.* ¶ Reading of the minutes. ¶ Papers of the evening: Tuberculosis in adolescents—a] Pathogenesis and clinical picture, Edith M. Lincoln; b] Treatment and prognosis, J. Burns Amberson, Jr. Discussion—Herbert R. Ed-

wards, Max Pinner, Lewis J. Friedman (by invitation).

FEBRUARY 25—*New York Pathological Society in affiliation with The New York Academy of Medicine.* ¶ Papers of the evening—a] Acute ulceration of the esophagus with associated intranuclear inclusion bodies, John M. Pearce; b] Malignant tumors of peripheral nerves, Arthur Purdy Stout (by invitation); c] Pathological findings in unexpected deaths in infancy and childhood, Jacob Werne. ¶ Executive session.

DEATHS OF FELLOWS

CALDWELL, WILLIAM EDGAR: 875 Park Avenue, New York City; born in Northfield, Ohio, February 23, 1880; died in New York City, April 1, 1943; graduated in medicine from New York University and Bellevue Hospital Medical College in 1904; elected a Fellow of the Academy January 3, 1918.

Dr. Caldwell was instructor and afterward assistant professor of obstetrics at New York University, 1908-19; associate professor of obstetrics and gynecology at the College of Physicians and Surgeons, Columbia University, 1919-27, when he was promoted to professor of clinical obstetrics and gynecology; consulting obstetrician and gynecologist to Presbyterian Hospital, New Rochelle Hospital and Monmouth Memorial Hospital; and associate director of Sloane Hospital for Women. He was a Fellow of the American College of Surgeons, the American Medical Association, a diplomate of the American Board of Obstetrics and Gynecology, and a member of the American Gynecological Society and the State and County Medical Societies.

DYKE, CORNELIUS GYSBERT: 706 West 168 Street, New York City; born in Orange City, Iowa, July 25, 1900; died in New York City, April 23, 1943; graduated in medicine from the State University of Iowa in 1926; elected a Fellow of the Academy November 7, 1935, and served the Academy as a member of the Committee on Admission from 1942 until his death.

Dr. Dyke was associate professor of radiology at the College of Physicians and Surgeons, Columbia University; attending radiologist to the Presbyterian Hospital; and director of radiology at the Neurological Institute. He was a Fellow of the American Medical Association, a diplomate of the American Board of Radiology, and a member of the American Neurological Association, the American Roentgen Ray Society, the American College of Radiology, the Harvey Cushing Society, and the State and County Medical Societies.

HABERMAN, JULES VICTOR: 156 West 86 Street, New York City; born in New York City, April 11, 1878; died April 9, 1943; received the degree of B.A. from Columbia University in 1902 and graduated in medicine from the College of Physicians and Surgeons in 1905; elected a Fellow of the Academy October 7, 1909.